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SOME OBSERVATIONS ON THE RELATIONS OF ESTROGENS AND PROGESTERONE TO THE CONTRACTIONS OF THE NONPREGNANT AND PREGNANT HUMAN UTERUS*

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MANY experimental studies have been devoted to the physiology of the myometrium both of human beings and of animals. Of these the most important have been made by Knaus in Europe and by Reynolds in the United States. The conclusions reached by these two observers regarding the relations of the estrogens and progesterone to the contractility of human and animal myometrium have been in almost complete agreement and have been very widely accepted by experimental workers and by clinicians. But some workers have been unable to accept their conclusions as they relate to the human myometrium and there is reason for believing that though their findings may be and probably are true of the rabbit uterus they do not apply to that of the human being. It is with the hope of clearing up some of the misunderstanding on this point that the following experiments and observations are presented.

Knaus[1-7] first studied the rabbit uterus using isolated muscle strips and concluded that in the nonpregnant state it was most active and responded most strongly to Pituitrin while under the influence of estrogen, whereas under the action of progesterone it became almost inert and Pituitrin could no longer stimulate it. During pregnancy he found the rabbit uterus to be inactive and without response to Pituitrin until the eighteenth day, when it began to regain both spontaneous contractility and its reaction to pituitrin; but though the former gradually increased, the latter remained depressed and only gradually returned to normal between about the twenty-seventh day and the onset of labor at the thirty-second day.

Reynolds[8-14] worked on intact animals, using a uterine fistula, and recording contractions through the medium of a bag and confirmed Knaus' findings for the rabbit's uterus.

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Support was lent to their conclusions by Corner and Allen[15] when they showed that in rabbits parturition could be delayed by injecting progesterone into the animals when they were nearly at term. Further confirmation was afforded by Snyder's[16] demonstration that administration of chorionic gonadotropin to rabbits shortly before term led to ovulation and the formation of corpora lutea whose secretion postponed the onset of labor.

Later Knaus[17, 18] studied the nonpregnant human uterus and concluded that it behaved as did that of the rabbit; that is, it contracted strongly and responded typically to Pituitrin in the follicular phase of the cycle and became inert and incapable of response to Pituitrin in the luteal phase.

At first Knaus' conclusions were disputed, but, reinforced by Reynolds, Corner and Allen, Snyder and others, they have been very widely accepted and theories of the cause and treatment of abortion, and of the cause of the onset of labor, have, among others, been based upon them. Yet, though Knaus' dictum has gained wide acceptance, the confirmation of his work has not rested on repetition of his experiments, but has been indirect, for Reynolds worked on intact animals, and Corner and Allen and Snyder's confirmatory conclusions were arrived at still less directly. However, his work on the human uterus has been repeated and amplified, and of those[19-21, 25-32] who have repeated it nearly all have wholly disagreed with his conclusions.

In 1943 the present writers[20] reported experiments on the nonpregnant human uterus in which the intrauterine bag and cannula described by Knaus[18] had been employed and the technique described by him had been followed. The conclusions reached were in complete disagreement with his.

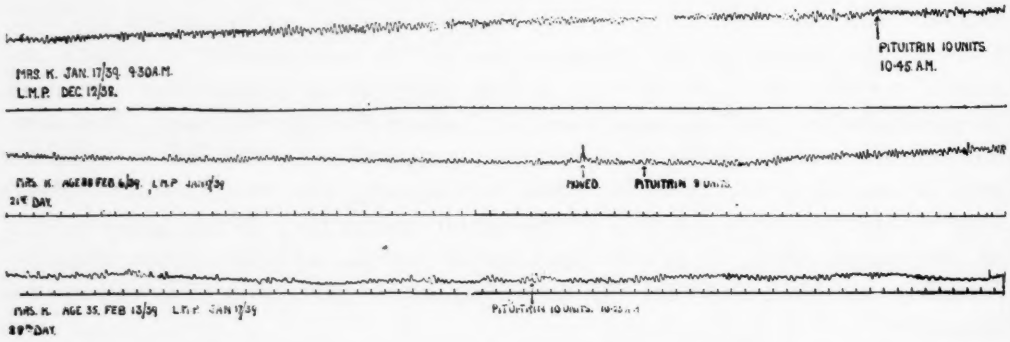
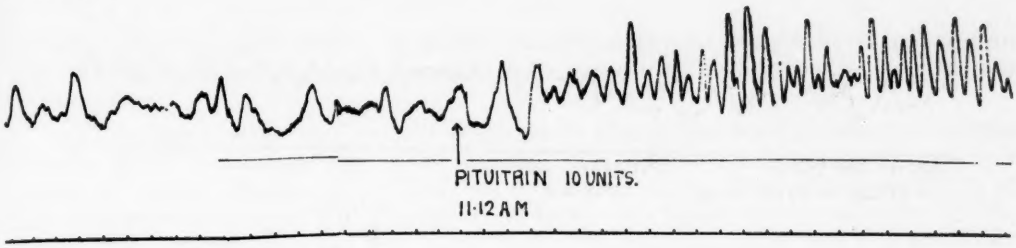


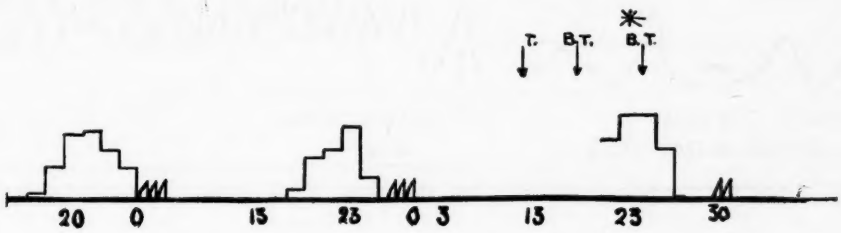
Fig. 1.—Tracings made from two anovulatory cycles of the same patient. The first and third were made at the end of the cycles; the second on the twenty-first day of the second cycle. Note the small, rapid, regular contractions and the very small response to Pituitrin.

At this time it is proposed to review some of these experiments and to add to them a number of others. Then, by comparing the tracings obtained in recording the contractions of the uteri of women whose cycles were normal with those of women whose corpora lutea were demonstrably abnormal and others in whom artificial cycles had been induced, it is hoped to offer a reasonable explanation of the results which we have observed.

The tracings in Fig. 1 were made in the second half of two anovulatory cycles, as judged by endometrial biopsies and the absence of pregnanediol excretion. The first and last tracings were made shortly before menstruation began. In them the contractions are small, rapid, and regular, and the effect of Pituitrin is very slight, as we have constantly observed in uteri under the influence of estrogen alone.

The second figure shows the uterine activity on the twenty-fifth day of a twenty-seven day cycle in which the function of the corpus luteum was normal





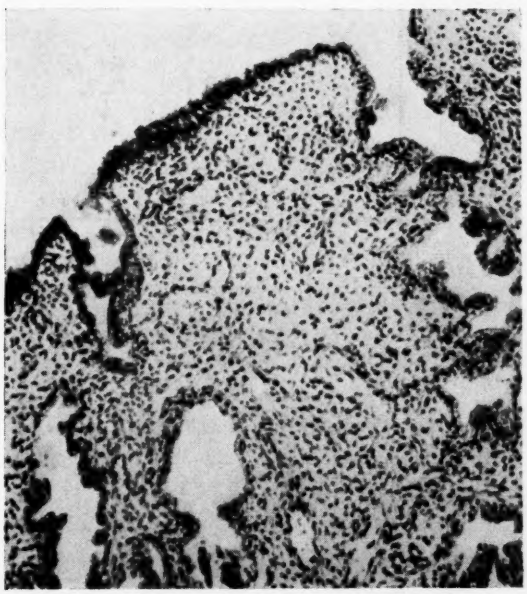
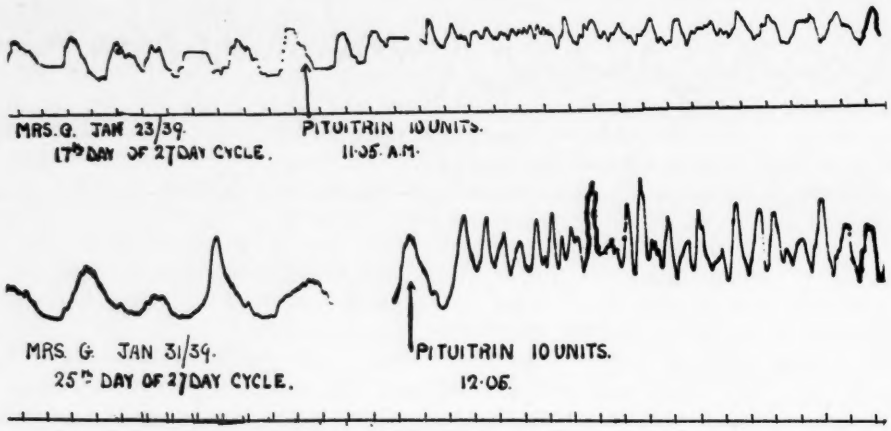
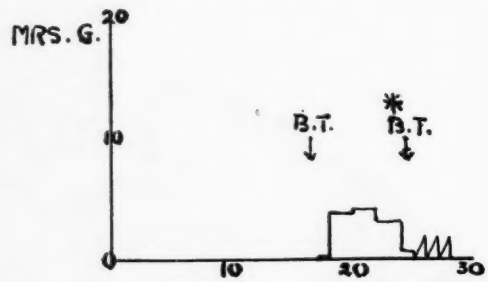


Fig. 2.—A tracing made on the twenty-fifth day of a twenty-seven-day cycle. Note the slow, strong, irregular, spontaneous contractions and the powerful response to Pituitrin.

as was shown by the level of pregnanediol excretion and the development of the endometrium on the day the tracing was made. The spontaneous contractions are slow and irregular and their amplitude is many times greater than that of those recorded when the uterus is influenced by estrogen alone. After the injection of Pituitrin their tone, frequency, and amplitude are all greatly increased, and they become remarkably regular. This type of spontaneous contraction and response to Pituitrin was seen repeatedly at or just before the end of normal cycles, and Moir[21] found it after the onset of menstruation.

In Fig. 3 the first tracing was made on the seventeenth day of a twenty-seven day cycle and the second on the twenty-fifth day of the same cycle. In the first the contractions are clearly not of the estrogenic type but belong to the luteal type though they are less completely developed than are those of the second, and the responses to Pituitrin in the two tracings have a similar





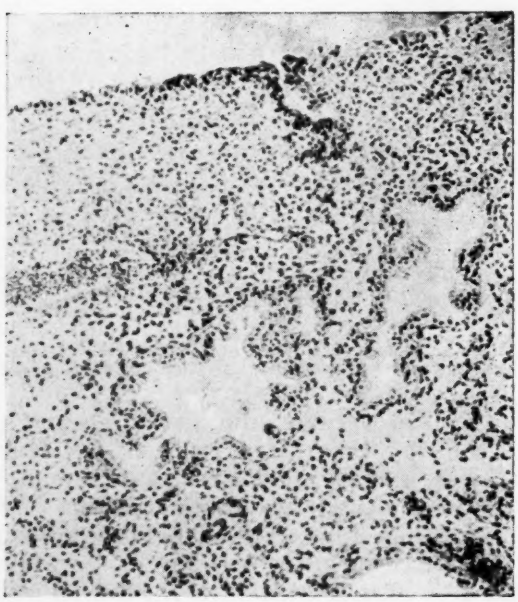
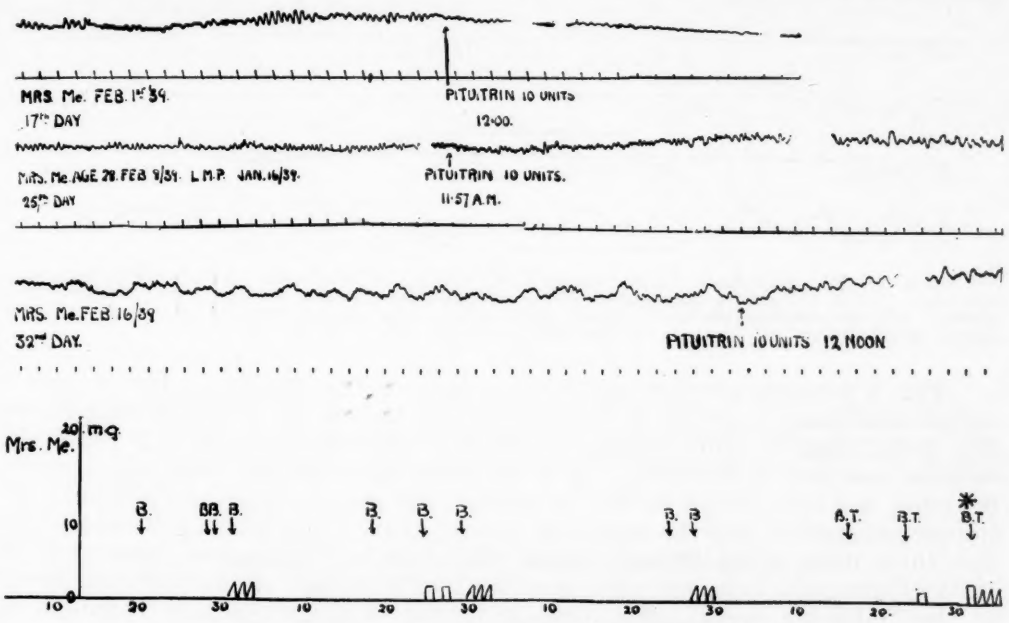


Fig. 3.—Tracings made on the seventeeenth and twenty-fifth days of a twenty-seven day cycle. Note the partially developed luteal type contractions in the first tracings as compared to the later tracing in the same cycle and to the late tracing in Fig. 2. The biopsy and the pregnanediol excretion suggest that the corpus luteum in this cycle may have been slightly deficient. This figure suggests that time is a factor in the development of full muscular activity.

relationship to each other. It would therefore appear that *time* is a factor in the development of maximal luteal type contractions and response to Pituitrin stimulation.

The woman who supplied the tracings in Fig. 4 had a very defective corpus luteum in all the cycles that were studied. In some no pregnanediol at all was excreted and in others only a little on occasional days. Her endometrium is of the progestational type but though the biopsy was taken on the last day of the cycle it is obviously very poorly developed. On this day there was a small excre-



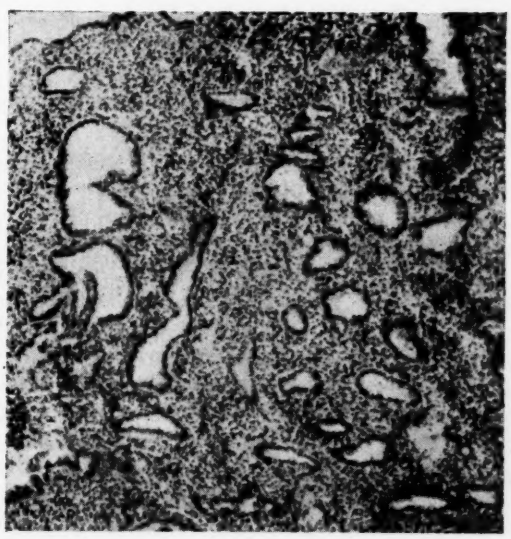


Fig. 4.—The tracings made in the same cycle of a woman whose corpus luteum was very deficient in secretion of progesterone as shown by pregnanediol excretion and biopsy. Note the early estrogenic contractions and in the last tracing made on the day before menstruation the poorly developed luteal type contractions (cf. Fig. 5). This suggests the necessity of adequate amounts of progesterone (and probably estrogen) for full muscular activity.

tion of pregnanediol. The first tracing on the seventeenth day is of the estrogenic type. The second on the twenty-fifth day perhaps shows a slight change toward the luteal type but it would be safer to call it estrogenic. The third on the thirty-second and last day of her defective cycle is definitely of the luteal type but the contractions and pituitary effect are poorly developed. They suggest that there is a *quantitative* relationship between the amount of progesterone available, (and probably of estrogen since this hormone is also secreted by the corpus luteum), and the development of the luteal type of contractions and response to Pituitrin.

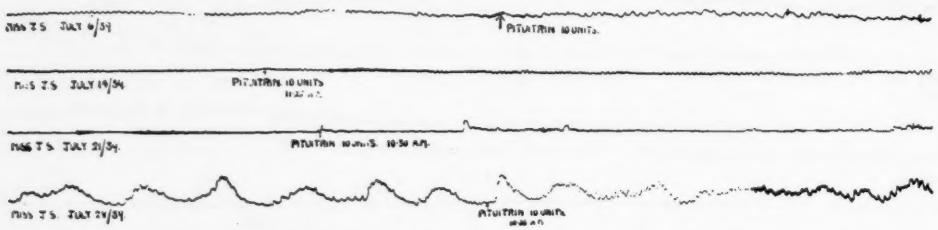


Fig. 5.—Tracings made during an artificial "cycle" in a woman whose ovaries had been removed. Note (1) the estrogenic type of contractions present before any estrogen was given; (2) the decrease in spontaneous contractility after large doses of estrogen; (3) the poorly developed luteal type of contractions (cf. Fig. 4).

Fig. 5 presents uterine contractions in an artificial cycle. This woman's ovaries had been removed about two months before the tracings were made. The rapid, regular contractions are of the estrogenic type with a small but definite reaction to Pituitrin. A week later after 100,000 units of estradiol benzoate had been given in two injections, the contractions and pituitary response are smaller and the same can be said of the third which followed a further three doses of 50,000 units each. The fourth followed two doses of 2,500 units of estradiol benzoate each combined with 10 mg. of progesterone given in the following week. The change in the contractions and response to Pituitrin is quite clear and both resemble those seen in the deficient luteal phase represented in Fig. 4. They suggest that both the quantity of the *hormones available* and the *time during which they act* on the myometrium are of importance in developing the typical luteal contractions.

The three remaining figures represent the activity, under the influence of artificially administered estrogen and progesterone, of the uterus of a 30-year-old married woman who had never menstruated. When first examined her uterus was so small that it could not be palpated apart from the small cervix. She was given fairly large doses of estrogen and it grew to have an internal length of 5 cm. and withdrawal bleeding was easily obtained. For this reason it was decided to give her a number of artificial cycles using both estrogen and progesterone in the luteal phases, the former in varying daily dosages and the latter in doses of 10 mg. per day. There were also variations in the length of the estrogen phase and of the luteal phase in some of the cycles. Withdrawal bleeding was obtained in all cycles. Mammary development was also easily induced. It was hoped to gain some idea of the quantitative relationships of estrogen and progesterone in the luteal phase of normal cycles and that she might be induced to have spontaneous cycles. We were not surprised to fail in the second purpose of our experiments but we had a measure of success in the first as may be seen in Figs. 6, 7, and 8.

In the cycle depicted in part in Fig. 6, the patient received 10,000 units of estradiol benzoate daily for ten days followed by 5,000 units of the same with 10 mg. of progesterone daily for nine days. The tracing made on the second day of combined estrogen and progesterone shows contractions of estrogenic type.

That made on the last day of the cycle shows typical luteal-phase contractions and response to Pituitrin as they are seen toward the end of a normal cycle (cf. Fig. 2).

In the next cycle shown in part in Fig. 7, 10,000 units of estradiol benzoate were given for ten days followed by 1,000 units of the same with 10 mg. of progesterone daily for four days. The tracing made on the third day of combined therapy shows early luteal activity and that made on the day after the last combined injection shows a better developed luteal type of contraction and pituitary stimulation, but they are not so fully developed as in the second tracing of Figs. 3 and 6, or in Fig. 2.

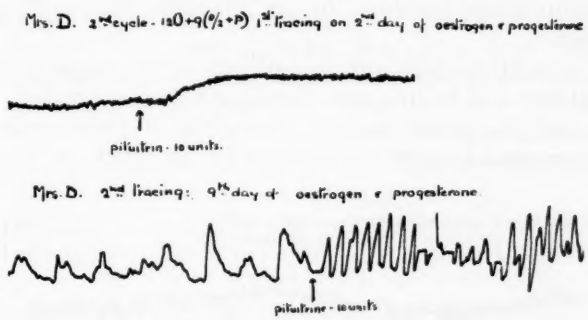


Fig. 6.—Tracings made in an artificial cycle of a 30-year-old woman who had never menstruated. In this cycle she was given 10,000 units of estradiol benzoate daily for ten days, followed by 5,000 units of estradiol benzoate and 10 mg. of progesterone daily for nine days. Note estrogenic type of tracing and response to Pituitrin on the second day of combined therapy; and the well-developed luteal contractions and pituitary response on the ninth day (cf. Fig. 2).

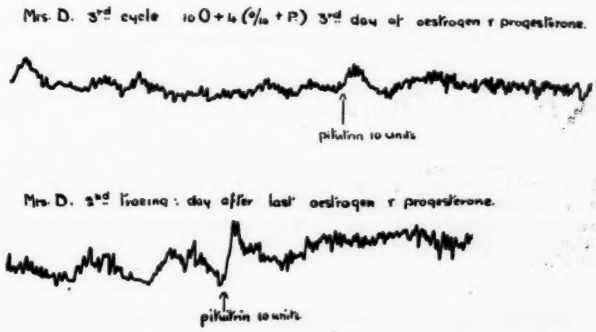


Fig. 7.—In this cycle 10,000 units of estradiol benzoate were given for ten days, followed by 1,000 units of the same with 10 mg. of progesterone for four days.

Note the very early luteal type of contractions in the first tracing and the somewhat better developed contractions of the same type the day after the last combined injection.

In the next cycle (Fig. 8), the patient received eight daily injections of 10,000 units of estradiol benzoate following which she was given 5,000 units per day for four days and for the same time took 100 mg. of pregneninolone daily by mouth. The first tracing of Fig. 8 shows the uterine activity on the second day of pregneninolone medication. The contractions are of the estrogenic type, though they are stronger than usual. The second was made two days later and shows an early and rather poorly developed luteal type of contractions resembling those seen in the defective natural luteal phase of Fig. 4 and the artificial cycle of Fig. 5. The third was made on the second day after the last administration of estrogen and pregneninolone and shows a further step toward the fully developed luteal type of contractions seen in Fig. 2.

If we compare these tracings which were made at different times in the luteal phase of normal cycles, cycles whose luteal phases are deficient, and artificial cycles we may draw the following inferences:

1. There is no inhibition of uterine contractility or sensitivity to Pituitrin in any of these cycles.

2. Estrogen alone does not increase uterine activity or render the myometrium more sensitive to Pituitrin, and Fig. 5 suggests that it is not essential to uterine contractions.

3. For the production of maximally efficient and typical luteal contractions such as occur at the end of a normal cycle, *both* estrogen and progesterone must act upon the myometrium *together, for an adequate time* and *in suitable quantities and proportions.*

4. If either or both is deficient in amount, or the time of their action is too short, the contractions will be less well developed than normal.

5. Estrogen and progesterone are synergistic in their action upon the myometrium. They are not antagonistic the one to the other.

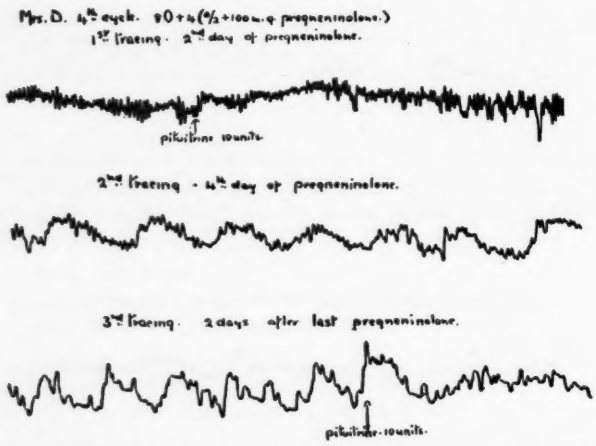


Fig. 8.—In this cycle 10,000 units of estradiol benzoate were given for eight days, followed by four days of half that dosage combined with 100 mg. of pregneninolone.

Note the slow development of luteal-type contractions and the resemblance of the second tracing to the last tracing of the deficient cycle in Fig. 4 and the last tracing of the artificial cycle in Fig. 5.

It has been contended that estrogen is essential for maximal efficiency of myometrial contractions and response to stimuli but it is difficult to find support for this point of view in the foregoing experiments, and their results are totally at variance with Knaus' conclusions.

It would appear from the first tracing in Fig. 5 that estrogen is not necessarily an important factor in the production of uterine contraction. This woman's ovaries were removed two months before the tracing was made. It is true that her adrenal cortex may have been producing a certain amount of estrogen, although almost certainly much less than that produced by a maturing follicle. But it is also true that after large amounts of estrogen her uterine contractions became smaller and this has also been seen in normal cycles. It therefore seems to us to be possible that the myometrium can contract and respond to Pituitrin in the presence of little or no estrogen.

It would seem probable from these experiments that neither estrogen nor progesterone alone will produce efficient uterine contractions either spontaneously or as a result of giving Pituitrin, but that there is an optimum proportion

of the two hormones, varying within as yet unknown limits and acting over an optimum length of time on the myometrium, which will produce a luteal type of contraction and response to Pituitrin, both of them of maximum efficiency.

If we consider the known actions of these two hormones on the histological development of the endometrium and myometrium we would expect the foregoing to be true. For we know that estrogens cause a proliferation of endometrial epithelium and stroma and Stieve[22] has shown that in the human cycle there is a production of new muscle cells in the myometrium. In the luteal phase of the cycle the combined effect of estrogen and progesterone on the endometrium is to transform the proliferated tissue gradually into the progravid state which involves secretory activity of the epithelium and early decidual changes in the stroma of the compact layer, and requires a definite length of time for its full development. Clauberg[23] pointed out that for the normal development of the cyclical changes of the endometrium, definite amounts and proportions of both estrogen and progesterone are necessary. Similarly he[24] has shown that in the luteal phase of the cycle of rabbits the myometrial cells increase greatly in size, both in length and in diameter, under the combined influence of the two hormones.

It is recognized that the efficiency of a muscle cell will vary according to its length and thickness before it begins to contract. It would therefore be expected that at, or just before, the end of a normal luteal phase the human uterus would have reached its maximum efficiency of contraction and response to Pituitrin, and this the experiments of Schultze,[25] Moir,[21] Robertson,[27, 28] and Kurzrock and associates[29, 30, 31, 32] make abundantly clear. Our own experiments,[20] reported in 1943 and in the present communication, lend support to the same conclusion and at the same time indicate a quantitative relationship between the two hormones and a harmonious synergistic action upon the myometrium leading to *maximal efficiency of its contractions at the moment when the uterus is physiologically called upon to expel its contents,* the unused progravid functional layer of the endometrium.

On the clinical side, there is general agreement that in the woman whose pelvis is free from tumors, endometriosis, or inflammatory disease, dysmenorrhea does not occur unless ovulation has occurred and a corpus luteum has been formed. Functional dysmenorrhea, therefore, appears to be associated with the maximum myometrial contractions which occur at the end of the cycle and the pain is probably due to some as yet undetermined disproportion between the estrogen and progesterone produced in the corpus luteum of the cycle that has just ended.

It is probable that the contractions of the myometrium are myogenic in origin; i.e., it is a function of uterine muscle cells to contract just as cardiac muscle cells contract spontaneously, and Stieve's[22] demonstration that the human myometrium is a syncytium somewhat resembling cardiac muscle supports this hypothesis. The spontaneous myogenic contractility of the myometrium is influenced by estrogen and progesterone which act in combination to produce maximal spontaneous activity and response to Pituitrin.

Since Knaus'[1-7, 17, 18] work it has been held that inhibition of the uterine contractions by progesterone permits the pregnant uterus to carry its contents to full term. This may quite possibly be true of the rabbit but it is not safe on that account to conclude that it is also true of the human being.

Knaus[1-7, 18] stated that in the pregnant rabbit the uterus is inert until the eighteenth day; from then until term spontaneous uterine contractions gradually increase and the response to Pituitrin slowly increases until the twenty-seventh day and more rapidly from then until labor begins. He also found degenerative changes in the corpora lutea of pregnancy and of the

decidua parallel to the changes in muscular activity. Allen[33] has shown that in the last two weeks of the rabbit's pregnancy the endometrium gradually changes from typical decidua back to an estrogenic type at term and it is known that at term there are mature follicles in the rabbits' ovaries and under normal circumstances the doe may be impregnated directly after delivery. It is therefore possible or even probable that in the rabbit the placenta has no endocrine function, and that the corpus luteum is the controlling factor and its gradual functional withdrawal is associated with the onset of labor.

On the other hand, the human placenta has an endocrine function and human pregnancy has two phases, the first controlled by the corpus luteum and the second by the placenta. In early pregnancy the secretion of the steroids is maintained at about the level set by the corpus luteum before implantation had occurred. The shift of steroid secretion from corpus luteum to placenta probably takes place gradually mostly in the second month of pregnancy and by about the seventieth day the excretion of estrogen and pregnanediol has begun to rise and continues to do so until term.

Owing to Knaus' dictum that progesterone inhibits the contractility of the pregnant uterus it has been felt that we must expect a fall in pregnanediol excretion before the onset of labor; and Lyon,[34] and Smith, Smith, and Hurowitz[35] have reported the consistent finding of such a fall at or near term. On the other hand Venning[36] and Browne[37] report that they can find no such change in either normal or abnormal cases at or near term, and Bachman[38] has made a similar observation. Venning and Browne find that pregnanediol excretion always rises irregularly throughout the last seven months of pregnancy and that labor may begin on a rising or falling excretion but that on an average there is a rise until the onset of labor. According to Venning[36] there also appears to be a relatively greater rise in the excretion of estrogen for some days before labor, and this confirms the findings of Marrian and Cohen.[39]

It appears to us that the human uterus is capable of spontaneous myogenic contractions throughout the greater part of its life, *and that its activity is greatest during the years of sexual maturity and reaches a maximum of efficiency at the two times when it is physiologically called upon to expel its contents, namely at the end of the normal cycle, and at the end of normal pregnancy.* We feel that the preparation for such maximal effort on these two occasions is almost certainly under the control of the same mechanism; that is, to reach such a state of efficiency requires the orderly synergistic action of adequate amounts of estrogen and progesterone acting in normal proportions and for sufficient time, but what actually sets the expulsive contractions in motion is still unknown.

When the uterus is called upon to expel its contents very prematurely as in abortion, the inefficiency of the whole mechanism is seen in the low pregnanediol output which may almost always be detected before the first symptoms of abortion occur and particularly in the inadequate uterine musculature which permits the dead products of conception to be carried for days, weeks, and even months before it is able to expel them; and even then the uterine action is so poor that exploration of the uterine cavity is almost always necessary to ensure that it is empty. We think that this indicates an incomplete preparation of the uterine musculature for the great expulsive efforts which it is prematurely called upon to make, rather than an inhibition of its contractions by progesterone.

The cause of the onset of labor is not known, and though we have argued that, up to the present, adequate evidence is not available to show that it is brought about by a cessation or marked diminution in the placental secretion of the steroid hormones, it must be at least probable that, just as the uterus is

prepared for its great expulsive efforts at the onset of menstruation and labor by the same hormonal mechanisms, differing in quantities of the hormones and in the duration of their actions, so the mechanism of the onset of expulsive contractions in each instance, whatever it may be, is also similar in nature, if not actually identical, except in degree.

Conclusions

1. Uterine contractions may be myogenic in orgin rather than neurogenic or hormonal, though proof of this awaits complete experimental evidence.

2. The uterus reaches its greatest muscular development and efficiency on the two occasions when it is physiologically called upon to expel its contents; namely, at the end of the normal cycle and at the end of normal pregnancy.

3. Maximal muscular efficiency is achieved by the harmonious synergistic action of estrogens and progesterone in the luteal phase of the cycle and throughout pregnancy.

4. Such muscular efficiency requires adequate amounts of the two hormones, in suitable proportions and acting for a sufficient length of time.

5. We know of no evidence that estrogen and progesterone are ever mutually antagonistic in their effects on the uterus.

6. The corpus luteum and the placenta secrete both hormones. Any therapy that aims at replacement of luteal function in the cycle or in pregnancy must therefore combine estrogen and progesterone.

7. Pregneninolone affects the activity of the myometrium and development of the endometrium in the same way as progesterone does, but it must be given in very large doses to produce comparable effects.

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Discussion

DR. FRANK O'LEARY, Toronto, Ont.—Dr. Henry has, I believe, proved his point beyond doubt of the effect of the ovarian hormones on the behavior of uterine muscle fibers. Proper ovarian hormonal balance should be the background of physiological uterine muscle contractions. I have wondered many times if this could be of help to us in our treatment of dysmenorrhea. Probably as a result of this work of Dr. Henry's we may yet arrive at a good understanding of and the solution to the problem of painful uterine contractions.

DR. E. M. ROBERTSON, Kingston, Ont.—I have never run across a textbook in which it is stated that the uterus contracts like the heart, but may I remind you of the saying of Dr. Chipman, that "the uterus is the pelvic heart." The original work of Knaus on uterine contractions has found its way down in the literature even to modern publications. I have repeated his work in the rabbit and the human being between 1936 and 1939 and have completely refuted his published statements. I agree with Dr. Henry that the corpus luteum phase of the menstrual cycle is not associated with complacence of the uterine muscle. The uterus can be more active in the corpus phase and much more sensitive to psychic stimuli. Pituitrin when injecetd intramuscularly takes four minutes to reach the uterus and I observe in Dr. Henry's tracings that the contraction response of the uterine muscle is almost coincidental with the injection of the drug. I believe this raises a clinical problem of dysmenorrhea being associated with psychogenic and psychosomatic problems. One cannot help but wonder how many pregnancies might be saved by the use of estrogen instead of corpus-luteum hormone in the treatment of threatened abortion. One can carry the parallel of the heart and the uterus further in the consideration of the blood supply of the musculature of each of these organs. The uterus must and does actually pump blood to its own muscle which needs it badly. In late pregnancy pregnanediol excretion becomes greater and greater right up to parturition and I agree that the highest level of excretion is at the time of the onset of labor.

DR. HENRY (Closing).—I do not believe that the actual expulsion of the products of conception in abortion is coincidental with the death of the fetus so that our hormone therapy in threatened abortion is probably of not much avail. I think there is a great field for further work in the problem of uterine contractions—work that will take many years to find all of the answers.

POSTPARTUM BLOOD LOSS: AN ANALYSIS OF 6,000 CASES*

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(From the Departments of Obstetrics and Gynaecology, University of Alberta Hospital)

IN A previous paper[1] we presented from the University of Alberta Hospital an analysis of volumes of blood lost during delivery in 2,000 cases. The series comprised 800 primigravidas in whom the blood loss averaged 388 c.c.: 1,200 multigravidas in whom it averaged 280 c.c., for a mean average of 323 c.c. Of this total there were 314 cases (15.7 per cent) in which the blood loss measured more than 600 c.c. In terms of blood loss over 1 per cent of body weight, the number was reduced to 205, or 10 per cent of the total. All these figures were higher than we had expected. We found that delivery through an episiotomy or lacerated perineum resulted in an average blood loss of 189 c.c. more than through an intact perineum, and where a side-wall vaginal tear occurred the amount increased to an even greater degree. Our data agreed with those of others that increased blood loss is related to: increase in the weight of the mother, the baby, or the placenta, prolonged labor, operative delivery, laceration or incision of the perineum, prolonged third stage, and ill-judged sedation.

At this time I propose to report an analysis of a further series of 4,204 cases comprising 1,791 primigravidas and 2,413 multigravidas, in whom blood loss during delivery and the third stage was measured in the same manner as detailed previously. In primigravidas the average measured 265 c.c., in multigravidas the average was 191 c.c., for a mean average of 219 c.c. One hundred eighty patients, or 4.3 per cent of this total, suffered blood loss of over 600 c.c. which figure, on the basis of loss over 1 per cent of body weight, is reduced to 128, or 3 per cent. We found, too, that episiotomy or laceration of the perineum occasioned an increased blood loss of 110 c.c. more than an intact vulvar orifice.

This is a gratifying decrease and has warranted enquiry into the factors which make for its occurrence. For this presentation a comparison of blood loss in relation to the duration of the third stage in both the previous and the present series, a description of the differences in the management of the third stage, and a comment on the effect of sedation will suffice. A comparison of other factors will be reserved for a future study.

In our earlier series (2,000 cases), Table I, only 176 primiparas (8.8 per cent) and 323 multiparas (16.1 per cent), or a total of 449 (25 per cent), were delivered of the placenta in less than 6 minutes following the birth of the baby. The greater number, 466 primiparas (23.3 per cent) and 757 multiparas (37.8 per cent), or a total of 1,223 (61.2 per cent), were in the third-stage interval of six to fifteen minutes. Thus 1,722 (86.1 per cent) of the 2,000 cases had a third

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stage of 15 minutes or less. Third stage duration was 16 to 30 minutes in 139 primiparas (7 per cent) and 109 multiparas (5.5 per cent), for a total of 248 (12.4 per cent) cases. In 24 cases (1.2 per cent) the third stage occupied 31 to 60 minutes, while in 6 cases (0.3 per cent) more than one hour elapsed before the delivery of the placenta. Blood loss in both primiparas and multiparas increased directly with the length of the third stage, together averaging 292 c.c. where the duration was under 6 minutes, increasing to an average of 529 c.c. where the duration was greater than 60 minutes. The one exception proved to be a multipara who retained the placenta for 6 hours, expelled it spontaneously through an intact perineum, and lost only 50 c.c. during the ordeal.

TABLE I. DURATION OF THIRD STAGE AND BLOOD LOSS PRIOR TO 1941, 2,000 CASES

	PRIMIPARAS		MULTIPARAS		TOTAL	
DURATION	NO.	AVERAGE BLOOD LOSS (C.C.)	NO.	AVERAGE BLOOD LOSS (C.C.)	NO.	AVERAGE BLOOD LOSS (C.C.)
Under 6 min.	176	378	323	245	499	292
6-15 min.	466	366	757	279	1,223	312
16-30 min.	139	450	109	369	248	415
31-60 min.	14	474	10	380	24	438
Over 60 min.	5	625	1	50	6	529
Total	800		1,200		2,000	

In our present series (4,204 cases), Table II, there were 1,319 primiparas (31.4 per cent) and 1,705 multiparas (40.5 per cent), or a total of 3,024 patients (71.9 per cent), who had a third stage of less than 6 minutes' duration. Where the third stage occupied 6 to 10 minutes there were 303 primiparas (7.2 per cent) and 467 multiparas (11.1 per cent), for a total of 770 cases (18.3 per cent). Thus, 3,794 patients (90.2 per cent) had a third stage of 10 minutes or less. Between 11 and 30 minutes there were 150 primiparas (3.5 per cent) and 212 multiparas (5 per cent), or a total of 362 patients (8.6 per cent). Twenty-six patients (0.6 per cent) took between 31 and 60 minutes to deliver the placenta, while 22 (0.4 per cent) took longer than one hour. The blood loss in both primiparas and multiparas in this series increased directly with the length of the third stage, together averaging 214 c.c. where the duration was under 6 minutes, and increasing, but only to 314 c.c., where the duration was greater than one hour.

TABLE II. DURATION OF THIRD STAGE AND BLOOD LOSS, 1941 TO 1947, 4,204 CASES

	PRIMIPARAS		MULTIPARAS		TOTAL	
DURATION	NO.	AVERAGE BLOOD LOSS (C.C.)	NO.	AVERAGE BLOOD LOSS (C.C.)	NO.	AVERAGE BLOOD LOSS (C.C.)
Under 6 min.	1,319	257	1,705	123	3,024	214
6-10 min.	303	280	467	203	770	233
11-30 min.	150	276	212	233	362	251
31-60 min.	10	335	16	238	26	275
Over 60 min.	9	322	13	307	22	314
Total	1 791	265	2,413	191	4,204	219

Pastore[2] has argued that blood loss volume should be considered in relation to the patient's body weight and has averred that over 1 per cent should be considered a postpartum hemorrhage. I have considered 600 c.c. as the topmost level of normal blood loss, although a patient of 100 pounds weight can lose

only 454 c.c., while one of 180 pounds can lose 816 c.c. and still remain in that category. An interesting contrast is recorded in Table III, where the incidence of postpartum hemorrhage in relation to duration of the third stage in each series is noted. Proper reference to the difference in time intervals should be made. In the early series 69 cases (3.45 per cent) occurring in the under-6-minute placental stage had postpartum hemorrhage while a relatively similar number, 115 (2.71 per cent), in the present series suffered a like fate. The 6- to 15-minute interval in the early series and the 6- to 10-minute interval in the present series provide a sharp contrast. In the former, 169 cases (8.45 per cent), or over one-half the total cases of postpartum hemorrhage, occurred during this time interval, while in the present series only 34 (0.8 per cent), or less than one-fifth, occurred. During the next interval, up to 30 minutes, the present series shows a marked reduction in numbers although the average blood loss is much the same. Where the third stage lasted up to one hour or longer, the present series shows a greatly decreased incidence and also a lower average blood loss.

TABLE III. BLOOD LOSS DURING DELIVERY. DURATION THIRD STAGE AND POSTPARTUM HEMORRHAGE

DURATION 3RD STAGE	EARLY SERIES		PRESENT SERIES	
	NO.	AVERAGE BLOOD LOSS (C.C.)	NO.	AVERAGE BLOOD LOSS (C.C.)
Under 6 min.	69	798	115	857
6-15 min.	169	828	34	821
16-30 min.	68	836	24	821
31-60 min.	6	967	2	800
Over 60 min.	2	1112	5	700
Total	314		180	839

The decrease in blood loss in the present series is so evident that one is immediately prompted to enquire as to the reason. Several factors, some of which have arisen during the time interval of this review, have, I believe, been largely responsible. They are detailed as follows:

A. Closer supervision of the pregnant patient's weight gain:

While the heavier patient can suffer a greater blood loss and yet remain below the 1 per cent of body weight volume, yet our experience has been that she has an increased tendency to a greater blood loss. Thus, her gain in weight should be kept within an optimum limit. Moreover, this supervision should commence at the patient's first visit and be diligently carried out during the succeeding visits.

B. A better evaluation of the patient's blood picture:

Plass, Bogert, and Stander, among others, have shown that there is blood dilution during pregnancy. While this is mainly plasma dilution, there must be consequently a relative decrease in red cell and hemoglobin volume. We have shown that a decrease in specific gravity of the blood serum is associated with an increased tendency to blood loss during delivery. Therefore it follows that a patient with a good relevant blood picture is less likely under ordinary circumstances to suffer severe postpartum blood loss. Many women during pregnancy suffer a hypochromic microcytic anemia, with hemoglobin values which decrease usually between the fourth and ninth months. Ferrous sulfate therapy alone is usually effective, as serum copper values increase tremendously during pregnancy and so preclude the need for copper ingestion as medication. Where the response to iron therapy is not satisfactory, recourse to blood transfusion during the third trimester would seem to be a reasonable procedure.

C. A more careful estimation of the patient's pelvic capacity during the last month of pregnancy:

An extremely tight fit because of bony or soft-tissue dystocia often results in severe blood loss during pelvic delivery, where, on the other hand, abdominal delivery would cause much less trauma. I do not advocate more abdominal sections, but I do feel that a well-considered indication is advantageous to both the mother and baby.

D. A more active management of the third stage:

Most texts teach that the third stage may last normally 5, 15, or 30 minutes and that no interference should occur until at least one hour has elapsed. They very properly note that there occur first separation and then expulsion of the placenta and agree on the mechanism. A review of the literature during the past ten years reveals a diversity of opinion regarding the management of this stage, but all agree that it has become unphysiologic, that some uterine stimulation should be used, that blood loss should be measured or computed, and that, if necessary, blood replacement by transfusion should be immediately effected.

I should like to note our experience in the management of the third stage. Before 1941 we were using, in turn, postpituitary extract (0.55 c.c.) intramuscularly, as soon as the baby was born, followed after delivery of the placenta by the intramuscular injection of 1 c.c. ergotamine tartrate. Later we injected them both immediately after delivery of the baby. In many cases there was a lull between injection and effect, wherein the uterus became atonic, the vagina filled with blood which was expelled, and abdominal uterine massage was necessary to stimulate uterine tone. This increased blood loss. Following the isolation of the ergonovine fraction in 1935, we used first a solution of ergometrine (The British Drug Houses) intramuscularly following the birth of the baby. Davis and associates[3, 4] in 1940 reported on the use of ergonovine (1 c.c.), intravenously injected, at the moment of the birth of the anterior shoulder. They noted that in 73 per cent of 1,020 cases the placenta was delivered in less than three minutes after the baby's birth and that no untoward result followed the injection. They advised against this procedure in breech delivery or following the delivery of the first of twins. Late in 1941 we adopted this routine and have continued its use.

Our procedure follows in some detail. As soon as the baby's head is born ergonovine (Ergotrate, Lilly) is injected slowly (25 seconds) intravenously. This causes a uterine contraction in 15 to 18 seconds. In the interval of waiting during the birth of the baby, any bleeding vessels in the perineum are clamped or tied off. Meanwhile the uterus has contracted down on the departing baby and has indeed remained in excellent tone. The placenta readily separates, the cord lengthens, and the placental edge is felt by the examining finger presenting through the cervix or in the vagina. The uterus meanwhile has become round and hard, has risen out of the pelvis up against the anterior abdominal wall, and is freely movable from side to side. It is grasped by the hand with the thumb in front and four fingers behind and used as a piston is pressed downward. The placenta quickly appears at the vulvar orifice, gentle traction on the cord is made, and the placenta is delivered by the Schultz mechanism. It is then twirled and the membranes trail in delivery like a twisted rope. The uterus, if it descends, is immediately elevated by placing the abdominal hand between uterus and symphysis and lifting, or by placing the vaginal hand against the anterior segment and pushing it upward. Once elevated it usually remains there in good tone. If it tends to relax, another 1 c.c. ampule of ergonovine is administered intravenously. If there is a history of uterine atony or of previous postpartum bleeding, intravenous glucose is commenced before

delivery, ergonovine (1 c.c.) is given directly at the birth of the shoulder and 1 or 2 c.c. are squirted into the solution to run in drop by drop. This I have found to be an excellent adjunct and obviates the need for immediate plasma or blood, although with the needle in place a quick change-over can be effected. The perineum if necessary is repaired after the placental stage is completed. Since the placental separation and delivery are so quickly and completely effected, uterine manipulation is at a minimum. This routine, not altogether original, is a modification of that described in part by Davis, O'Connor, and Dieckmann, who all reported satisfactory results. If the placenta is slow to separate, interference is unnecessary as long as there is no bleeding. If bleeding occurs then we do not hesitate to remove the placenta manually. Following manual removal, and/or where there is the threat of uterine atony, the vagina is packed for 16 to 24 hours. We believe packing to be of value and have had no untoward results in the 24 instances in the early series and the 23 in the present series (total 47 or 0.75 per cent) where it has been employed.

E. A change in the routine of sedation:

In 1941 we stated that, in our opinion, while sedation had a definite place in the conduct of labor, yet somnolence was preferable to unconsciousness and the peak should be reached during the first stage. At that time we were using a mixture of barbiturate by mouth (Nembutal) and paraldehyde by mouth or rectal injection. Our awakening resulted from several causes, shortage of nursing, intern, and attending staff and a greater number of younger mothers whose labors were shorter. The barbiturate dosage was decreased, hyoscine replaced the paraldehyde, and Demerol was added in June, 1942. In 1944 we inaugurated a program of early ambulation, one which would not have been possible with our previous routine of sedation. In reviewing the charts, the decrease in blood loss parallels these changes. For the past five years we have used barbiturates by mouth and Demerol and hyoscine intramuscularly (or occasionally intravenously) during labor, and, for delivery, nitrous oxide and oxygen, cyclopropane and oxygen, low spinal or local pudendal block.

But equally important, I believe, has been a late change in our method of conditioning the patients to the physical discomfort of labor. It has involved a quiet discussion with the patient, at some time during the second and reiterated during the third trimester, of the various forces involved in the mechanism of labor and their causal relationship to the "pains" which will occur. It has involved also a routine of both physical and mental relaxation for the patient during the antenatal period, which she can carry over into the intrapartum state and so obviate the fear-pain-tension syndrome aptly described by Read. It has indeed actually decreased the need for tremendous sedation. With this routine the immediate postpartum apathy has vanished and the patient is eager to be up and about early, a circumstance which up to the present has been productive of excellent results.

Summary

There has been presented:

1. A review of a previous series of 2,000 obstetrical cases in which the measured blood loss during delivery averaged 323 c.c. with 314 cases (15.4 per cent) in which it measured 600 c.c. or more.

2. A review of a present series (4,204) cases in which the measured blood loss averaged 219 c.c., with 180 cases (4.3 per cent) in which it measured 600 c.c. or more.

3. A comparison of the duration of the third stage in relation to blood loss, of the two series, showing a greater number in the present series with shorter duration and consequently less blood loss.

4. A brief note on the reasons for the decreased length of the third stage and decreased blood loss, i.e., supervision of antenatal weight gain, attention to the patient's blood picture, pelvic capacity estimation, more active management of the third stage, and a change in intrapartum sedation.

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Discussion

DR. ROSS MITCHELL, Winnepeg, Man.—In the years 1938 and 1939 all maternal deaths in Manitoba were carefully reviewed and it was found that hemorrhage was the greatest cause of maternal mortality. I agree with what Dr. Vant has said as to the relationship of the blood loss and the duration of the third stage of labor. The more or less recent introduction of the use of ergot intravenously after the birth of the head or shoulders has, I am sure, lessened the amount of blood loss. I do not believe, however, that the placenta will come quite as quickly as has been said. In my experience it takes from 8 to 10 minutes after the administration of intravenous ergot. I believe that the third stage of labor should be terminated by manual removal of the placenta when any woman is losing more blood than she can stand. Lives have been lost by waiting too long. With better technique and the added help of good anesthesia, I am sure that the risk of infection from manual removal can very largely be forgotten.

DR. VANT (Closing).—There are several arguments against the use of ergot intravenously at the end of the second stage, the important one being that you cannot follow this procedure in home deliveries. This is not a very valid argument against the use of the drug, since in Edmonton about 95 per cent of maternity patients are delivered in hospital. There are a few points to remember when using ergot intravenously. Most important of these is that it should be injected slowly, taking at least 25 second to inject 1 c.c. It has been thought that some patients might go into shock following injection, but I have never found this. I have found, on the contrary, that the blood pressure will rise about 20 points and that this will last from 20 to 25 minutes. I think that the obstetrician should wait at least half a minute after injection before continuing the birth of the baby. The uterus will then contract and come down on the departing baby. I think this is very important and I believe further that the cord should not be cut until pulsation stops, that is, from 1 to 2 minutes after the delivery of the baby. This continuity of events allows separation of the placenta and prevents incarceration.

A REVIEW OF 500 ELECTIVE OPERATIONS FOR PELVIC PROLAPSE ON WOMEN OVER THE AGE OF 60 YEARS*

A. C. G. Frost, Vancouver, B. C.

(From the St. Paul's and Vancouver General Hospitals)

THE gynecologist of today is being confronted more and more with the problem of the elderly woman as a surgical patient. Fifty years ago, the average age of life was 50; today, the life expectancy of the white American woman is 68.6[1] and some authorities say that it soon may reach 75 years.

Another reason why we are seeing an increasing number of these women is the changing of the times. Gone are the days when grandmother was satisfied to lead a sedentary life at home, to knit and sew by the hour.

The elderly woman of today insists on taking an active part in society. She drives her car, she travels, she gardens or plays golf, and invariably is active in some sort of church or welfare organization. She reads the latest magazines where she is informed of various advances in medicine and surgery pertaining to her age. She seeks your advice after diagnosing her own prolapse. She has probably had this complaint for years but now it is beginning severely to incapacitate her, so much so that she is being forced more and more into a most inactive life. She may be 60, 65, 70 years old, or more.

The purpose of this investigation is to attempt to determine whether we are justified in subjecting this elderly but apparently healthy woman to operation and what are the risks entailed in such a procedure.

Material

The case histories of 500 women from 60 to 83 years of age were studied. One hundred seventy-four of these were taken from the records of St. Paul's Hospital and 326 from the Vancouver General Hospital. Of these 500 cases, 62, or 12.4 per cent, were staff and 438, or 87.6 per cent, were private cases. We began in February, 1948, and took all consecutive cases of elective operations for pelvic hernias on women 60 years and above until we had collected 500 cases. This covered a period of eleven years—not a large number of cases when one considers that these hospitals care for 90 per cent of the population in a city of 300,000.

As it is only the mortality, morbidity, and complications in these elderly women that are under investigation, no follow-up results are tabulated, as it is considered that the risk is evaluated by the time the patient is discharged from hospital. One, however, was re-admitted four weeks after operation with phlebitis and pulmonary embolic phenomena, and survived. There may have been others with similar accidents.

As these are all elective operations, therefore, no cases of malignancy, polyp, leucoplakia, fistulas, nor fibroids have been included.

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*Presented at the Fourth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Niagara Falls, Ont., June 26 to 28, 1948.

Table I shows the age incidence. Of these, approximately half the patients were over 65 years of age.

TABLE I. AGE INCIDENCE (60 TO 83 YEARS)

60-64	65-69	70-74	75-79	80-84
257	164	58	18	3
51.4%	32.8%	11.6%	3.6%	.6%

These 500 operations were performed by 75 different doctors in the city. About 45 per cent were performed by surgical specialists and general practitioners combined.

TABLE II

GYNECOLOGISTS	SURGEONS	GENERAL PRACTITIONERS
275	130	95
55%	26%	19%

Table III shows the clinical pelvic findings. As these diagnoses have been made by many doctors, one cannot expect them to be as accurate as if a group of gynecologists had alone recorded their findings. No doubt some degree of prolapse existed where cystocele and rectocele alone were recorded. Also, stress incontinence and enterocele probably were more frequent than noted.

TABLE III. CLINICAL PELVIC FINDINGS

	NO.	%
First and second degree prolapse with cystocele and rectocele	238	47.6
Cystocele and rectocele	89	17.8
Complete prolapse	76	15.2
Cystocele with or without incontinence	27	5.4
Cystocele, rectocele, incontinence of urine	25	5.0
Cystocele, rectocele, prolapse, incontinence, urine	25	5.0
Cystocele, rectocele, enterocele	9	1.8
Enterocele only	6	1.2
Rectocele only	5	1.0

Table IV shows the incidence of hypertension. Sixty-two and eight-tenths per cent showed some sort of hypertension, with 39 per cent having a blood pressure over 170 systolic. Hypertension is common in women over 60 years of age and in itself is not a contraindication to surgery if there is no cardiac nor severe renal damage present.

TABLE IV. BLOOD PRESSURE

	NO.	%
Normal	133	26.6
Systolic 141-170	166	35.2
Systolic 171-200	101	20.2
Systolic 200 and above	47	9.4
Total No. with hypertension	314	62.8
Not recorded	53	10.6

Table V shows the incidence of significant medical conditions. This list is probably incomplete as some histories and physical examinations were very uninformative. On the other hand, patients with serious medical complications would not be subjected to surgery.

On only 13 charts were varicose veins noted and three of these patients died of embolus. No doubt many more did have varicosities which were not noted.

There were two women who, after operation, informed the nurse of lumps in the breast, which turned out to be carcinoma.

TABLE V. INCIDENCE OF SIGNIFICANT MEDICAL CONDITIONS

	NO.	%
Diabetes	10	2.0
Varicose veins	13	2.6
Bronchitis	2	.4
Myocarditis	9	1.8
Arthritis	2	.4
Rheumatic heart disease	2	.4
Latent syphilis	2	.4
Pyelonephritis	1	.2
Toxic thyroid	1	.2
Auricular fibrillation	1	.2
Pernicious anemia	1	.2
Tuberculous endometritis	1	.2
Carcinoma of breast found after plastic operation	2	.4
Carcinoma, ovary found after plastic operation	1	.2
Diverticulosis	2	.4
Asthma	1	.2
Senility	2	.4
Breast amputation 13 days prior to plastic	1	.2

Table VI shows the type of operation performed. It will be noted that suspension of the uterus was performed in fifty-six of the cases with prolapse, by the surgeons or general practitioners. This procedure, in my opinion, is unwarranted for this condition.

TABLE VI. TYPES OF OPERATION

	NO.	%
Repair of cystocele and rectocele	149	29.8
Repair of cystocele and rectocele, amputation of cervix	145	29.0
Vaginal hysterectomy	57	11.4
Watkins' interposition	26	5.2
Repair of cystocele only	26	5.2
Cystocele, rectocele and uterine suspension	43	8.6
Cystocele, rectocele, enterocele	10	2.0
Suspension only	7	1.4
Cystocele, rectocele, amputation cervix, and suspension	6	1.2
Rectocele only	9	1.8
Cystocele and amputation of cervix	6	1.2
Cystocele and suspension	2	0.4
Rectocele and suspension	4	0.8
Enterocele only	3	0.6
Rectocele, supravaginal hysterectomy	3	0.6
Le Fort operation	4	0.8

It will also be noted that vaginal hysterectomy was performed in only 11 per cent of cases, probably because the surgeon and general practitioner do not feel competent to do this type of operation.

Table VII shows the type of anesthesia used. It will be seen that 58.9 per cent of these patients received ether, and 27.6 per cent spinal. In comparison to the practice in other centers, local anesthesia was seldom used, only fifteen patients receiving this anesthetic.

TABLE VII. TYPES OF ANESTHESIA

		NO.	%
Ether		195	39.0
Avertin and ether	294 or 58.9%	77	15.4
Amytal and ether		22	4.5
Spinal		138	27.6
Cyclopropane		47	9.4
Local		15	3.0
Pentothal		4	0.8
Cyclopropane and curare		2	0.4

Table VIII shows the number of days in hospital prior to operation. Seventy-seven per cent of these patients were operated upon the day after admission. The overcrowding of our hospitals during the war years may have accounted for some of this. Staff patients were usually in hospital more than several days before operation.

TABLE VIII. DAYS IN HOSPITAL PRIOR TO OPERATION

	NO.	%
One day	387	77.4
Two days	35	7.0
Three days	23	4.6
Four days	14	2.8
Five days	7	1.4
More than 5 days	34	6.8

Table IX gives a list of the complications. There were four deaths, all probably due to embolus, which will be discussed in detail. There were 52.0 per cent with no complications.

TABLE IX. POSTOPERATIVE COMPLICATIONS

	NO.	%
Deaths	4	0.8
Normal	260	52.0
Fever, no definite cause	98	19.6
Postoperative shock	28	5.6
Perineal infection	20	4.0
Pneumonia	8	1.6
Mild upper respiratory infection	5	1.0
Peritoneal infection	5	1.0
Pelvic infection	7	1.4
Phlebitis	5	1.0
Pulmonary embolus	6	1.2
Postoperative cervical hemorrhage	2	0.4
Rectovaginal fistula	2	0.4
Vesicovaginal fistula	1	0.2
Auricular fibrillation	2	0.4
Broad ligament hemorrhage	1	0.2
Erysipelas	1	0.2
Hepatitis	1	0.2
Abdominal wound	1	0.2
Intestinal obstruction due to carcinoma of ovary	1	0.2
Urinary infection	13	2.6

There were 98 patients, or 19.6 per cent, who had a temperature of 100.4° F. or above after the second postoperative day, for which no definite cause could be ascertained from the doctors' or nurses' notes.

There were twenty-eight cases of operative shock.

Definite pneumonia occurred in only eight cases with a milder upper respiratory infection in five. No doubt some of these patients did have upper respiratory infections but this fact was not noted in their charts.

Phlebitis was noted in five nonfatal cases.

Pulmonary embolus occurred in six cases. Four of these were fatal and two were not. Of these two nonfatal cases, one patient, aged 61 years, had had a curettage, and repair of cystocele and rectocele and was discharged on the eighteenth postoperative day apparently well. She returned to hospital four weeks later with a phlebitis of the leg and showing pulmonary embolic phenomena from which she recovered. There may have been other such patients readmitted.

The second case was that of a woman of 65 years who had had varicose veins with phlebitis fifteen years ago and it was noted that she still had varicose veins on admission. She had had a cystocele and rectocele operation done and on her fifth postoperative day, while in bed, went into shock with cyanosis; breathing was rapid and labored with feeling of tightness across the chest. She was placed in oxygen for twenty-four hours and gradually improved, was up in chair on her thirteenth day and discharged on fifteenth postoperative day apparently well. No electrocardiograph nor x-ray of the chest was taken.

Discussion of Deaths

MRS. H. T.—Apparently she developed a small embolus on her fourth postoperative day, again another on the twelfth postoperative day, and the fatal one on the seventeenth day after operation, which was proved by autopsy.

As autopsies were not performed in the other three deaths, we can only surmise the cause.

MRS. J. M.—The patient gave a history of varicose veins. There were no other complications and, in getting out of bed on the seventh postoperative day, she died suddenly. Death was probably due to embolus rather than to coronary occlusion.

MRS. L. D.—Developed a cough on the fourth postoperative day, otherwise her postoperative course was normal. She was up daily from the fifth postoperative day until the eighth day when, while walking, she collapsed and died one hour later. Although coronary disease cannot be ruled out, embolus probably was the cause of death.

MRS. H. S.—Was up on the day of operation, developed a wheezy cough and distention on the second postoperative day. On the sixth day after operation she complained of pain in the right leg which also was swollen. She appeared to be well on the eleventh day, when she was discharged, and suddenly died the same day while walking up the steps of her home. Again embolus likely was the cause of death.

No anticoagulation therapy was administered to any of these patients. In one early ambulation therapy was carried out.

One wonders, if prophylactic antithrombotic treatment had been started immediately after operation, whether these patients would have been saved. Also, in these elderly women with severe varicosities, would it be advisable either to refrain from surgery or to carry out a ligation of the veins prior to operation?

In the hospitals in which this series was done, during plastic operations, the patient's feet are suspended by a figure-of-eight strap. No saddle rest is used under the knee but there is the possibility of pressure to the calf of the leg against the metal upright. This, however, is padded with sponge rubber.

Comment

Because of the prolongation of the life of the average American woman and because these elderly women insist on being more active than their sisters

of a few decades ago, we gynecologists are being called upon more and more to relieve these women of their symptoms surgically. Although a cystocele, rectocele, or prolapse in itself will probably not shorten a woman's life, it certainly will cause marked discomfort and pain, and confine her in many cases to a most sedentary life.

As Lash has stated, the surgical risk in the older woman has not been properly answered. Previously it was thought that these patients withstood anesthesia and operative procedures very poorly and as a result curative surgical treatment was withheld because of their age. Of the six leading gynecologists of this city who have been practicing throughout this period under review, five of them did an average of 15.8 private cases in eleven years—or just over one case per year—the sixth man did 78. I think this shows that we are still reluctant to operate on these women.

Brumm and Williams[2] reported 257 patients with severe coronary disease who were operated upon for various emergency surgical reasons with a mortality of 4.3 per cent from cardiac causes.

Goldsmith[3] states that these elderly people do have many complications such as hypertension, renal and cardiovascular disease, but yet these conditions in themselves were not sufficient to contraindicate surgery.

Kosmak[4] has put it aptly when he says that a woman is as old as she looks and that it is preferable to measure old age not by years but by competency, both physical and mental; the patient's outlook on life and her mental state are most important factors to be considered when selective surgery is contemplated.

In this series, very few blood chemistry examinations, electrocardiographs, and roentgen studies were done to ascertain cardiovascular and renal conditions.

If a patient has no symptoms such as edema, shortness of breath, nor precordial pain, one may assume that she has sufficient cardiac reserve, but I do feel that with all these easily available facilities at hand, we should have these studies done in a large proportion of cases prior to operation.

The low rate of respiratory complications, 2.4 per cent, and postoperative shock, 5.6 per cent, with no deaths in these conditions, to me is most illuminating. Of the four patients who died, three had varicose veins of the legs. One was up on the day of operation, one up on the fifth postoperative day.

Early ambulation on the first and second postoperative day and the prophylactic antithrombosis treatment might lower the incidence of embolus, the bugbear of gynecological surgery.

Summary and Conclusions

1. Five hundred elective operations for pelvic hernias on women over 60 years of age have been reviewed.

2. There were four deaths, or a mortality rate of 0.8 per cent.

3. The operative risk more than offsets the comfort and relief afforded these more or less incapacitated women.

4. Many older women apparently are not being operated upon by gynecologists because of age.

5. One should be hesitant in operating upon those with marked varicosities of the legs.

6. The question of prophylactic anticoagulation therapy should seriously be considered in pelvic operations on these elderly women.

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Discussion

SIR WILLIAM FLETCHER SHAW, Manchester, Eng. (By invitation).—This paper brings out points in which I have a special interest. We should make it a rule to operate only on people who have been in the hospital for at least one full day before operation and only after thorough physical examination. I am not sure I can agree that we are now operating on more old people than we used to. In Manchester there is a considerable number of women with prolapse. We have always followed the idea that age did not matter and that the condition of the individual was a more important criterion for operation. Women of 50 years are sometimes older than others of 70. With care most elderly patients came through well and without embolism. In my own experience a small number of women died of pulmonary embolism. Proper preoperative care might have eliminated a considerable number of those. I do not believe that suspension operations or vaginal hysterectomy have any part in the treatment of prolapse of the uterus.

DR. W. F. ABBOTT, Winnipeg, Man.—I did not notice any mention of blood levels or weight levels in this group of cases. I have found a lowered hemoglobin level of greatest significance, especially in pulmonary embolism. In a series of 300 cases with six deaths, five of them were due to pulmonary embolism. This occurs, of course, especially in the older age group. I believe that when the hemoglobin level is lowered, it should be raised by appropriate measures before operation.

THE MANAGEMENT OF THE OCCIPUT POSTERIOR*

The Use of the Bill-Scanzoni Maneuver

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THE occiput posterior position long has been a cause of concern. Its etiology, incidence, and management have been discussed at considerable length and contributions made to its management by Bill,[1, 2, 3, 4] Caldwell,[5] Calkins,[6, 7, 8] Corbet,[9] Cosgrove,[10] D'Esopo,[11] Dodek,[12] Gustafson,[13] Hennessy,[14] Keettel,[15] Kushner,[16] Manley,[17] Moore,[18] Murphy,[19] Reddington,[20] Simpson,[21] Tatelbaum,[22] Thoms,[23] Vaux,[24] and others. In great part these have been reports from American clinics. In order to assess its frequency, and obtain some consideration of its importance as a problem in Canadian obstetrics, those cases occurring in my practice have been reviewed.

Material Studied

Incidence, Parity, Position.—

The occiput posterior position occurred on 244 occasions in the course of 1.817 deliveries of all presentations, an incidence of 13.4 per cent. One hundred and seventy-eight had been followed prenatally; 66 were referred for opinion and delivery by other physicians; 14 were delivered after consultation by their own attendants, and 5 were excluded from considertion as they occurred in the second baby of twin pregnancies. Two hundred and twenty-five labors and deliveries were supervised and conducted personally. Of the 225, 154 were in primiparas and 71 in multiparas. Right occipitoposterior occurred in 121 instances; left occipitoposterior in 104. The incidence of primary posterior positions varies greatly in published reports and this is readily understandable as it depends upon the stage of labor, when the first examination is made, and the care with which it is conducted. All patients studied were examined abdominally and rectally or vaginally; in a considerable number, radiological examinations were utilized to assist in conduct of prolonged or difficult labor and substantiated the diagnosis.

TABLE I. MATERIAL STUDIED

Total deliveries			1,817
Occiput posteriors:			
Personal cases	178		
Referred cases	66		
		244	13.4%
Delivered by others	14		
Second babies of twin pregnancies	5		
		19	
Labors supervised or conducted personally		225	
Parity:			
Primiparas	154		
Multiparas	71		
Position:			
R.O.P.	121		
L.O.P.	104		

*Read at the Fifth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper Park, Alberta, June 19 to 21, 1949.

Etiology.—

Various explanations have been offered for the occurrence of the occiput posterior presentation. The association of this position with greater or lesser degrees of pelvic contraction has been emphasized by Vaux and Cosgrove. Thoms, D'Esopo, Caldwell, and others have done much with their radiological investigation to explain the etiology, mechanism of labor, and proper management in the specific types of pelvic architecture which they find associated with this abnormality. On the contrary, Calkins considers that the posterior position is normal and occurs with similar frequency as anterior positions. The Chicago group drew attention to the frequency of its occurrence in patients of the dystocia dystrophy type; in the present report six patients fell in this group. Twenty-one had bony pelvic abnormalities in the form of minor midpelvic and outlet contractures, while five had major bony abnormalities necessitating cesarean section for cephalopelvic disproportion. Other less obvious abnormalities of pelvic form probably occurred without being noted. The importance of these lesser aberrations from normal is hard to assess in the small number of cases presented here. It is reasonable, however, to suppose that if it was of great significance, previous or subsequent labors would present similar problems. In forty-nine patients in whom accurate records of other labors were available, forty-five had had anterior positions, whereas four had two posterior labors.

Length of Labor.—

The great majority of reports state that labor in the occiput posterior is materially prolonged in comparison with that of the occiput anterior. In this group of cases the durations of labor are noted in Table II.

TABLE II. LENGTH OF LABOR

Average of All Cases.—	
Primiparas:	
1st stage	24 hours, 25 min.
2nd stage	1 hour, 20 min.
Multiparas:	
1st stage	11 hours, 56 min.
2nd stage	51 min.
Referred Cases.—	
Primiparas:	
1st stage	40 hours, 2 min.
2nd stage	2 hours, 17 min.
Multiparas:	
1st stage	36 hours, 10 min.
2nd stage	2 hours, 41 min.
Personal Cases.—	
Primiparas:	
1st stage	20 hours, 54 min.
2nd stage	1 hour, 20 min.
Multiparas:	
1st stage	9 hours, 34 min.
2nd stage	57 min.

The longer duration of the first stage of labor in referred cases in both primiparas and multiparas is remarkable and difficult to explain unless these were cases which provided greater difficulty with dilatation due to uterine inertia or cervical resistance which Calkins believes may be present in many posterior positions. It is unlikely that such complications should be found in referred cases only, though no doubt consultations were obtained only in instances which caused concern for the attendant by undue prolongation of the course of labor.

Course of Labor.—

Spontaneous rotation to the anterior position can be anticipated in a great proportion of posterior presentations. In 225 labors this occurred 108 times, 10 were terminated as midtransverse arrests, and 107 remained as persistent posteriors. This figure is some what higher than those usually cited but considerably lower than those of the advocates of immediate delivery with the beginning of the second stage. The combination of uterine inertia and cervical dystocia was frequently noted, occurring 16 times. In general this was overcome by rupture of tough membranes late in the first stage. The persistence of an intact bag of membranes was a more constant finding than that of early or premature rupture. It occurred 35 times, in contrast to premature rupture which occurred 12 times. The maintenance of intact membranes in cases where there was no evidence of disproportion and dilatation had progressed to 4 to 6 cm. seemed to impede rather than to facilitate progress. Murphy and Calkins have paid considerable attention to the character of pains and consistency of the cervix in relationship to the length of labor in posterior position. The former could demonstrate no significant tendency for poor contractility to occur in posterior positions, which is in contrast to the general belief that the labor pains are ineffectual or weak in many posterior positions and account for failure of progress and rotation. He found disproportion a more significant cause of nonengagement than poor contractility and could find no evidence that the latter affected the direction of rotation in the occiput posterior. Calkins, too, feels that, given similar station, pains, and cervical consistency, the duration of labor is not appreciably lengthened in posterior position. He believes that the inability of a patient to deliver herself spontaneously when the position is posterior is due to other factors than the position itself. Bill, however, believes that the position per se is abnormal and recommends its correction as soon as full dilatation occurs. Weight and size of babies are not thought to influence the course of labor in posterior positions.

Management.—

All authorities are agreed upon the conserative management of the first stage; interference prior to full dilatation is unwarranted. Vaginal delivery under such circumstances may, and frequently does, lead to disaster. In rare instances incision of the cervix may be required to make vaginal delivery feasible; this or manual dilatation was necessary in three cases. The latter procedure is not as satisfactory in my hands as incision. Failure to achieve full dilatation, or progress beyond dilatation of 4 to 6 cm. after prolonged labor with ruptured membranes, usually indicates some cephalopelvic disproportion. In these, extraperitoneal section is to be preferred to any form of vaginal delivery in the interest of both mother and child. This procedure was performed upon two occasions where the disproportion was not recognized sufficiently early to justify the transperitoneal operation.

In general, the plan of management followed was conservative in the first stage with maintenance of fluid intake intravenously if necessary. Sedatives were used freely and given on indication. In my experience the rational use of sedation has never made uncomplicated labor complicated. In many instances, indeed, it has seemed to give a much needed relaxation with subsequent progress. This was noted in six instances in referred patients.

The management of the second stage is much more controversial. As such a large proportion of posterior positions rotate spontaneously, conservative management is supported by many obstetricians. This varies with the individual, but in general, from two to four hours in second stage is considered sufficient for spontaneous rotation and delivery. In contrast to the conserva-

tive treatment, Bill, Miles, and Vaux advocate interference as soon as the first stage is completed. Should rotation become necessary, manual rotation is most widely advocated. The use of Kielland forceps is preferred by Cosgrove, Miles, Kushner, Manley, and others. Bill and his disciples feel the modified Scanzoni maneuver to be the most acceptable technique when the head is engaged; with unengaged heads, internal podalic version is the method of choice where no disproportion exists. It is with respect to the soundness of this view that this paper is concerned. The technique is simple and the ease with which rotation can usually be obtained is such that its wider use is deemed justfiable. The fundamental feature of Bill's modification is rotation, without traction, at the level of arrest. Briefly, it consists in the following steps, the usual requirements for forceps delivery having been achieved.

1. Application of the blades as for an anterior position with correct cephalic exactitude. (Depression of the handles before locking facilitates this.)

2. After locking, the handles are raised toward the opposite groin of the patient which favors flexion of the head.

3. The handles are then swept through a wide circle which maintains the blades of the forceps in the same axis during rotation and the fetal head turns with them with little force on the part of the operator. The progress of rotation may be followed by placing the fingertips of the free hand upon the lambdoid sutures.

4. On completion of rotation slight downward traction fixes the head in the anterior position.

5. Removal of the blades and reapplication in the anterior position with traction completes the delivery.

Thorough dilation of soft parts or generous episiotomy facilitates the procedure. The virtues of the technique are the ease of rotation and the lack of necessity for disengagement of the head to permit rotation. The risk of extensive vaginal lacerations in the Scanzoni maneuver has been exaggerated. Simple twisting of the handles will produce a wide arc of rotation of the blades with resultant damage to soft parts, which has led to the belief that this is inherent in the method. The use of solid-bladed forceps facilitates introduction, application, rotation, and extraction. The Tucker-McLean forceps with the Bill axis-traction handle fulfills all the requirements for this purpose.

Method of Delivery.—

In the 225 cases considered here, spontaneous rotation occurred in 108 instances with delivery as shown in Table III.

In 107 persistent posteriors the Scanzoni maneuver was used in 86 instances. The rotation was performed at the following pelvic levels: midpelvic 7, low midpelvic 20, and low pelvic 59.

Internal podalic version was performed 5 times. Cesarean section was required in 9 cases, an incidence of 3.7 per cent in comparison with a general incidence in all presentations of 4.6 per cent. In 5 of these cases the indication was cephalopelvic disproportion. In the remaining 4, a combination of cervical dystocia and uterine inertia, without gross disproportion, was the indication for abdominal delivery. Of the patients sectioned, 2 were elderly primiparas. The child was delivered by choice as a posterior in 6 instances and once inadvertently when the position was unrecognized. These posterior deliveries were spontaneous, with wide episiotomies or operative deliveries carried out early in practice when suitable forceps for rotation were not always available.

In the 10 midtransverse arrests, rotation and delivery were accomplished in 8 instances with a single application of Tucker-McLean forceps. In 2 Tarnier forceps were used for extraction following anterior rotation.

TABLE III. METHODS OF DELIVERY

A. Spontaneous Rotations.—			
High midforceps		2	
Spontaneous		5	
Midforceps		5	
Low midforceps		33	
Low forceps		63	
			108
B. Midtransverse Arrests.—			
Single application and rotation		10	
			10
C. Persistent Posteriors.—			
Internal podalic version	5		
Face to pubis	7		
Cesarean section	9		
		21	
Modified Scanzoni.—			
Midforceps	7		
Low midforceps	20		
Low forceps	59		
		86	
			107
			225

Fetal Results and Complications.—

In all, 6 babies were lost, a gross mortality of 2.6 per cent. Of these, 2 deaths occurred in the 178 deliveries which were personally conducted throughout by me. One of these was a hydrops fetalis which had rotated spontaneously. The other occurred in a hydrocephalic with craniotomy, version, and breech extraction. In the 4 remaining instances, shoulder dystocia in large babies was probably responsible; in 2, though, the labors had been excessively prolonged and in one of them the fetal heartbeat could not be heard at the time of consultation. Rotation was accomplished in these instances by the Scanzoni maneuver without difficulty. In the remaining 2, manual rotation had been at-

TABLE IV. FETAL MORTALITY AND MORBIDITY

Stillbirths.—			
Hydrops fetalis	1		
Hydrocephalus with craniotomy	1		
Prolapse of cord	1		
Prolonged labor, difficult delivery of shoulders	2		
		5	
Neonatal Deaths.—			
Atelectasis, insufflation of amniotic fluid, prolonged second stage	1		
		1	
			6
Morbidity.—			
Shrill cry (cerebral damage ?)	1		
Fracture of humerus	1		
Erb's palsy	1		
Congenital amputation of hand	1		
Hematoma of cheek	1		
Pyloric obstruction	1		
Asphyxia (slight)	3		
		9	

tempted and failed in one case; in the other, prolapse of the pulseless cord had been present for some time prior to consultation. These deaths might have been avoided by earlier consultation or less energetic attempts at manual rotation.

Other fetal complications were noted as follows: one baby with a shrill cry suggesting cerebral damage, apparently well at discharge; one congenital intrauterine amputation of hand; one hematoma of cheek; one pyloric obstruction and three sluggish infants requiring intratracheal intubation to stimulate respiration.

Maternal Complications and Morbidity.—

There were no maternal deaths in this series. Sulcal lacerations occurred in 17 instances; cervical laceration in 1 instance. Excessive postpartum bleeding was noted in 17 cases; 6 of these were cases of shock and 4 required transfusion. Premature separation of placenta occurred 3 times. The anal sphincter was partially incised or lacerated in 13 instances and the rectum was incised once in performing episiotomy. No disability was experienced from the latter complications.

TABLE V. MATERNAL COMPLICATIONS

Sulcal lacerations	17	
Cervical laceration	1	
Laceration of anal sphincter	13	
Incision of Rectum	1	
Postpartum hemorrhage	17	
Premature separation of placenta	3	
		52

Morbidity statistics were incomplete but 12 or 5.3% of mothers showed elevations of temperature in the puerperium of significant nature due to the causes shown in Table VI.

TABLE VI. MATERNAL MORBIDITY

Pyelitis	5	
Phlebitis	2	
Mastitis	1	
Breast abscess	1	
Pelvic cellulitis	1	
Pulmonary infarct	1	
Unknown	1	
		12
		5.3%

There was no apparent difference between the morbidity of patients delivered vaginally who required rotation and those who had rotated spontaneously.

Comment

The problems presented by the occiput posterior position in the present series are similar to those reported from American sources. The association of dystocia seems significant but not greatly different from that experienced in other cephalic presentations. Indeed, the incidence of serious dystocia requiring cesarean section is less than in all other reports. The occurrence of apparent disproportion due to the position, however, is not infrequent. Nonengagement should occasion less concern than that occurring in occiput anterior positions, were the deflexion attitude cannot be held accountable for the findings. True disproportion at the brim is more to be anticipated when the head is floating in primiparous patients with anterior positions than in those with

posteriors. The association of deficiencies in the powers and resistance in the cervix and membranes accounted for a considerable delay in labor. The artificial rupture of membranes when dilatation has progressed to or beyond 4 to 6 cm. almost invariably hastened completion of the first stage and is recommended when bony disproportion has been excluded. Interference and attempted vaginal delivery before full dilatation of the cervix are to be condemned. The use of Voorhees bags to hasten or complete dilatation, manual dilatation, or incision of the cervix were not used extensively and are not recommended. Abdominal delivery by the extraperitoneal route is to be preferred to difficult vaginal delivery, in the face of a persistent cervix, as the latter is exceedingly traumatic to both mother and child.

Abnormalities in pelvic conformation accounted for a considerable proportion of primary posterior presentations but only on rare occasions did they occasion major dystocia. The occiput posterior itself occasioned dystocia or at least delay in labor in many instances which was readily overcome by the use of the modified Scanzoni maneuver. That the position itself, rather than other factors such as pelvic abnormality, or inadequacy of the powers, was responsible in these instances was suggested by the rapid advance, descent, and delivery following correction of the malposition. The simplicity and ease with which the engaged head may be rotated by the modified Scanzoni technique suggests that its wider employment in Canadian obstetrics might prove useful.

The size of the baby, while not significantly altering the course of labor, did make for difficulty in delivery in some cases. There seemed to be a slight tendency to an abnormal frequency of large babies in posterior positions as compared with the findings in other presentations.

Summary and Conclusions

1. A report upon 244 occiput posterior presentations and labors in 1,817 consecutive deliveries is here presented.

2. There was no maternal mortality and a gross fetal mortality of 2.6 per cent is reported.

3. The occiput posterior position occasioned some delay in labor where bony and cervical dystocia were frequently associated with unruptured membranes and uterine inertia. These complications were no greater than those encountered in anterior positions.

4. Noninterference, in the first stage, except artificial rupture of membranes, with the adequate use of sedatives and maintenance of fluid balance, is mandatory to successful progress.

5. The wider employment of the Bill modification of the Scanzoni maneuver is suggested as an advance in the management of the persistent posterior when engagement has occurred.

6. Earlier consultation and interference in the second stage of labor are justifiable and advantageous for mother and baby.

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Discussion

DR. T. R. CLARKE.—As Dr. Cannell has pointed out, the incidence of primary posterior position varies greatly in published reports. For a long time it has been our feeling that something more than a simple statement of the position at the onset of, or during, labor is necessary for an informative analysis of statistics on the subject. That is to say, we do not feel that inclusion of all cases which happen to be, or to have been, occiput posterior during labor will give us a true view of the problem, or, to put it another way, there are occipitoposteriors and occipitoposteriors.

However, we are the first to admit the difficulties of establishing the criteria by which a case might be classified as OP, OP2, OP3 or any other designation we might choose in classifying the clinical behavior of these cases. Dr. Cannell has pointed out that "various explanations have been offered for the occurrence of occipitoposterior presentation." This statement implies differences of opinion and negates to a large extent an etiological approach to a subclassification, but we will not give up our contention that some workable subclassification would be of value in assessing the various methods of dealing with dystocia associated with occiput posterior.

We have long been plagued by consideration of the cause and effect relationship in regard to occipitoposterior. Is poor flexion a result or a cause of occipitoposterior? We have made use of the Hodge maneuver, which has as its object increasing flexion with resultant spontaneous internal rotation, suggesting that lost flexion is a cause of occipitoposterior. Lost flexion may account for the clinical syndrome of nonengaged occiput posterior. Our experience indicates that cases in which flexion is maintained or increasing are those in which spontaneous internal rotation may be anticipated.

No one will deny the contribution of those who have pointed out the importance of pelvic architecture in relation to posterior positions. Our difficulties have been encountered from the spine down. We are not aware of a version having been done for nonengaged occipitoposterior in our vicinity. We simply do not encounter this type of dystocia. Even with unfavorable pelvic architecture we have not been able to abandon the impression that given good pains and good flexion, nature will sometimes accomplish natural delivery of a posterior.

In regard to disproportion as a cause of occipitoposterior, we can only say that some of our most trying cases have occurred where we have felt certain of an adequate cephalopelvic relationship. It is probably fair to say that some people are prone to see the root of all obstetrical evil in disproportion. Admitting the pitfall of unrecognized disproportion, we are not disposed to attribute our occipitoposterior difficulties to this etiological factor.

It is in relation to the forces, to uterine action, that our major difficulties have arisen. Are poor pains with resultant prolonged first stage the cause or the result of occiput posterior? Our feeling is that in the majority of instances this is an accidental association, the occiput posterior being neither the cause nor the result of poor pains. That is to say, we would expect to encounter prolonged first stage as frequently with anterior positions, with few exceptions, these comprising the dystocia dystrophy syndrome and the odd instance where in the face of a prolonged first stage posterior rotation from the anterior position has occurred.

Our chief difficulties have arisen in connection with prolonged first stage, and, call it what you may, deficient uterine motility, cervical resistance, incoordinate uterine action, to us the root of the problem lies in a better understanding of uterine physiology and pharmacology. We have made very frequent use, as has Dr. Cannell, of rupture of the membranes at about one-half dilatation, and have, as he has, been frequently gratified with the results. We still have those cases in which dilatation is much prolonged and we are not able to agree that this "usually indicates some cephalopelvic disproportion," at least not a disproportion of a degree that would not have been overcome with an anterior position, this latter consideration indicating the pathological potential of the posterior position per se.

We are in accord with Dr. Cannell when he advocates noninterference in the first stage, except rupture of the membranes. We have felt that in many instances progress is favored by ever so little manual dilatation at the time of rupture of the membranes—a little manual encouragement, if you like. Another device which we have successfully utilized is the application of Willett's scalp traction forceps well toward the occiput to encourage flexion, increase the effectiveness of contractions, and so hasten full dilatation.

Dr. Cannell has indicated the importance of sedation and it would have been interesting to have heard him expand the statement "never in my experience has the *rational* use of sedation made uncomplicated labor complicated." Too much too early or too little too late seem to be the crucial considerations in this regard.

Dr. Cannell has reported four fetal deaths in sixty-six referred cases in which the average first stage was thirty-eight hours, against two unavoidable fetal deaths in one hundred seventy-eight personal cases. This is an enviable record. The importance of the length of labor in relation to the fetal result is reocgnized and our feeling is that intrauterine death can and does occur in the face of a prolonged first stage, this without cephalopelvic disproportion as a factor.

The controversial views on the management of the second stage have been excellently summarized by the essayist. Our attitude has been conservative to the extent of preferring to await spontaneous internal rotation within two hours of full dilatation. The problem seems to hang on the consideration of when obdurate conservatism becomes obtuse radicalism.

When interference is indicated, the question arises as to whether there is one method of choice or whether different situations permit or demand different handling. Generally the method with which one is most familiar will give him the best results. Argument against widespread application of the Scanzoni manuver in skillful hands is difficult to produce. We feel with Dr. Cannell that the principle of rotation at the level of arrest is fundamental. In transverse arrest we have abandoned the usual forceps in favor of Barton's forceps, but we rarely complete delivery with them. As a matter of fact, as an outgrowth of experience, the majority of our midpelvic rotations are done with Barton's instrument, after manual rotation to the transverse, which is usually easily accomplished.

We have found occipitosacral positions particularly likely to result in stress incontinence and tend to interfere early in such instances.

In regard to face to pubis position, our feeling is that if delivery is imminent it may be permitted, its undesirability having been perpetuated in textbooks which have not taken cognizance of modern episiotomy. Rarely it may be preferable to deliver as face to pubis with forceps, pelvic architecture being the basis for this.

In regard to cesarean section, Dr. Cannell has resorted to abdominal delivery in four instances for "a combination of cervical dystocia and uterine inertia without gross disproportion." These represent the resolution of most difficult problems and are the fruit of obstetrical judgment. We are all agreed on the importance of getting the cervix out of the way. Bags, manual dilatation, and incision of the cervix are rightly condemned.

It is a good principle in young women that cesarean section places their obstetrical future in jeopardy. If we adhere strictly to this principle, an occasional baby will be sacrificed on the block of obstetrical axion. We have no doubt that Dr. Cannell has wisely chosen the abdominal route in those instances in which it has been elected.

OBSTETRICAL MORTALITY IN EDMONTON FOR TEN YEARS (1939-1948)*

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THE material under analysis comprises the obstetric deaths in the City of Edmonton during the ten years, 1939 to 1948.

All patients under consideration were confined in one of five institutions: the four general hospitals in the city and a "lying-in home" for unmarried mothers, which is situated on the outskirts of the city. The four city hospitals are the University Hospital with a medical Superintendent and with a "closed" staff, the Royal Alexandra Hospital with a medical Superintendent and with an "open" staff and the General and Misericordia Hospitals, each under the direction of a Sister Superior and each of which is open to the profession at large. The medical staff of the "home" known as Beulah Home is comprised of general practitioners and it is the policy of its administration and staff to transfer to one of the hospitals in the city all cases in which complications arise or are anticipated.

It should be mentioned, too, that only rarely is a patient confined at home in Edmonton and if she is it is usually because of the urgency of the situation which precludes transfer to a hospital before delivery occurs.

For the purpose of this discussion all deaths from abortion and ectopic pregnancy were excluded.

General Results

In this ten-year period, 42,559 women were confined in the five above-mentioned institutions with a total of thirty-eight fatalities, a gross mortality rate of 0.85 per 1,000 births. Included in this total, however, are two deaths occurring before the end of the first trimester as it is felt these fell within the scope of this study. The first of these patients died from acute necrosis of the liver after a five-day illness; the second from hyperemesis gravidarum after thirteen days in hospital.

Of the total number of deliveries 1,184 (2.78 per cent) occurred in Beulah Home, and although no deaths actually occurred in this institution, three of the thirty-eight deaths (7.9 per cent) were in patients transferred from it to hospitals in the city either after delivery or in one case immediately before delivery. The latter patient died of bronchopneumonia within one and three-fourths hours of admission to hospital; another was transferred with acute inversion of the uterus, and a third with puerperal sepsis. The mortality rate thus for patients in Beulah Home was 2.5 per 1,000 births.

The mortality rate for the entire group by five-year periods was: 1939, 43 = 1.2 per 1,000 births; 1944, 48 = 0.69 per 1,000 births; with a ten-year average of 0.85 per 1,000 births.

*Presented at the Fifth Annual Meeting, Society of Obstetricians and Gynaecologists of Canada, Jasper Park, Alberta, June 19 to 21, 1949.

TABLE I

YEAR	TOTAL DELIVERIES	NO. DEATHS	MORTALITY RATE PER 1,000 BIRTHS		TOTAL NO. CESAREAN SECTIONS	CESAREAN SECTION % RATE
1939	2,802	5	1.78		31	1.1
1940	2,993	5	1.64		20	0.68
1941	3,216	3	0.93	Av.	32	1.0
1942	3,510	1	0.28	1.2	29	0.82
1943	4,016	6	1.49		62	1.54
1944	4,175	5	1.2		57	1.36
1945	4,620	5	1.08		89	1.92
1946	5,389	5	0.92	Av.	75	1.39
1947	6,003	1	0.16	0.69	145	2.41
1948	5,835	2	0.34		151	2.58
Total	42,559*	38†	0.85		691	

*Delivered in lying-in home = 1,184.

†Including three transferred from lying-in home, and two deaths before end of first trimester.

Classification and Frequency of Causes of Death

In several instances more than one factor contributed to the fatal termination of the case, so for the sake of simplicity the deaths were classified from the standpoint of the chief etiological factor under the following five headings:

1. Hemorrhage and shock, comprising all cases in which either hemorrhage alone or hemorrhage associated with obstetric trauma was the paramount factor, a total of nine cases.

2. Toxemia, including all cases in which were manifested any or all the triad of hypertension, proteinuria, and edema, i.e. pre-eclampsia and eclampsia, hypertensive disease and nephritis, but excluding the cases of acute necrosis of the liver, eight cases.

3. Coincident cardiac disease, six cases.

4. Puerperal sepsis, four cases.

5. Miscellaneous, including pulmonary embolus—3, necrosis of liver—3, bowel obstruction—1, bronchopneumonia—1, anesthesia—1, iso-immunization to the Rh factor—1, secondary carcinoma—1.

The order of frequency of these groups of causes is set forth in Table II, from which it is noted that hemorrhage and shock head the list, accounting for 24 per cent of the total deaths. It is worthy of note, however, that, in the Royal Alexandra Hospital with the largest service, no deaths from this cause have

TABLE II

CAUSE	NO. DEATHS	% OF TOTAL	
Hemorrhage or shock	9	24%*	
Toxemia	8	21%	
Cardiac	6	16%	
Sepsis	4	10%	(none since 1944)
Misc.†	11	29%	
Total	38	100%	

*In one hospital no deaths from hemorrhage and shock in last 15,662 deliveries over past eight years.

†Miscellaneous:

Pulmonary embolus	3
Necrosis of liver	3
Bowel obstruction	1
Bronchopneumonia	1
Anesthesia	1
Blood transfusion	1
Secondary carcinoma	1

occurred in the past eight years in 15,662 deliveries. It is interesting, too, to learn that cardiac disease is the third commonest cause of death, and that there has not been a death from sepsis since 1944.

Preventability.—

In attempting to assess whether or not any given fatality is or is not preventable, the writer fully realizes that any one individual's assessment may be falacious; but an attempt has been made to use the terms "preventable" and "nonpreventable" in a liberal sense, having in mind that all the facts pertinent to a case may not have been available in the records.

In general then, those classified as preventable included all cases in which it is felt that adequate and timely medical care could have saved the life of the patient, and into this group fall most of the cases of hemorrhage and shock, of the so-called "toxic" group, the patient with hyperemesis who succumbed after thirteen days in hospital, and the one patient with bowel obstruction which occurred after delivery who died in the operating theatre on the second postpartum day.

Included in the "nonpreventable" category were all cases in which it was felt adequate care was provided after the patient sought advice, as well as several which might be classified as being "questionably preventable." The whole group included such cases as pulmonary embolus, necrosis of the liver, all the cases of cardiac disease, some of the "toxic" cases, reaction to blood transfusion, unrelated metastatic carcinoma, and bronchopneumonia. On this basis the deaths were categorized as follows:

TABLE III

HOSPITAL	PREVENTABLE DEATHS	NONPREVENTABLE DEATHS
A	7	8
B	5	4
C	6	1
D	3	4
Total	21	17

Assuming this to be a fair assessment, with seventeen nonpreventable deaths out of a total of thirty-eight, we might have attained a mortality rate of 0.38 per 1,000 births instead of 0.85.

Cesarean Section.—

It was felt that some mention should be made of any influence that cesarean sections might have had on the over-all results. From Table I, it is apparent that the section rate has increased during this ten-year period, varying from a low rate of 0.66 per cent in 1940 to 2.58 per cent in 1948. It will be noted also that the rate definitely exceeded 1 per cent in 1943 and that it definitely exceeded 2 per cent in 1947. Referring again to the mortality rates, it is apparent that in the past five years with the cesarean rate increasing, the mortality rate in any one year has not been greater than 1.2 per 1,000 births, and, the cesarean section rate reaching 2 per cent, the highest mortality rate was in 1948 when it was 0.34 per 1,000 births. Moreover, it should be mentioned that in the last two years with the section rate over 2 per cent, no deaths have resulted from hemorrhage and shock, nor in any "toxic" cases.

During this ten-year period a total of 691 cesarean sections were performed with two deaths, one from pulmonary embolus on the fifteenth postoperative day, and one from hemorrhage and shock following section for placenta praevia. In the past nine years there have been no deaths in the last 660 sections.

Hemorrhage and Shock.—

Of the total of nine fatalities in this group, four occurred in one hospital. In three of the nine, hemorrhage alone was the cause, although one of these

patients died following hysterectomy after all other means had failed to control the bleeding.

It is regrettable that in reviewing these nine cases we find evidence of so much "bad obstetrics." Among the contributing factors are: manual dilation of the cervix, version through incompletely dilated cervix, failure properly to attend the third stage of labor in a spontaneous delivery, failure to transfuse early, failure to pack early, failure to diagnose and institute treatment early in placenta previa, failure to make proper use of diagnostic aids such as the x-ray in the antepartum period and during labor, use of high forceps, repeated unsuccessful attempts at vaginal delivery, failure to obtain adequate consultant advice and operative aid, failure to inspect the genital tract completely for evidence of lacerations, site of hemorrhage, etc., failure to provide adequately for supportive care of the patient in long labor and prepare for the hemorrhage and collapse which may follow, and failure to institute *early* replacement of blood lost until the protective mechanism of the patient has begun to fail.

Other important factors are: uselessness of saline and glucose infusions to replace gross blood loss, disparity between amount of blood that different patients may lose and onset of symptoms of shock, almost certain fatality from rupture of the uterus, and danger of anticipating a spontaneous cessation of bleeding.

Having all these factors in mind, it is of particular interest to learn that these patients survived from one to eleven hours after the onset of hemorrhage or the occurrence of obstetric trauma, and that the average elapsed time was four and one-half hours—a period sufficiently long in which to salvage a life if treatment is prompt and decisive.

Toxemia.—

Of this group which totalled eight in number, five and possibly a sixth patient suffered a cerebral hemorrhage, and, of the group, two cases were diagnosed as eclampsia, one convulsive and one nonconvulsive. It is felt that five of the total of eight were preventable.

Study of this group reveals the following contributing factors: failure to give adequate antepartum care, failure to recognize the danger of toxemias and hospitalize the patient, failure to emphasize the danger to the patient and to insist on hospitalization, failure to attempt adequately to prevent postpartum convulsions (for example, one patient developed convulsions twenty hours post partum), failure to terminate pregnancy at the optimum time, and failure to attend adequately known severely toxic patients during labor.

Coincident Cardiac Disease.—

This group constituted 16 per cent of the total. All these deaths were classed as nonpreventable, although it appears that in some cases the seriousness of the cardiac lesion was not appreciated, and that, in some, adequate cardiac consultations were not obtained, or at least were not recorded. Time does not allow discussion of the value of such procedures as a routine chest x-ray and other procedures as aids to the diagnosis of pre-existing cardiac lesions and their management during pregnancy.

Liver Necrosis.—

This very serious condition was the cause of three fatalities and was a factor in a fourth. No specific therapy is as yet known for the acute fulminating form of the disease, although our newer knowledge of the physiology of the liver and recent work on the treatment of pathologic physiology gives us hope that we may someday be able to prevent it.

Anesthesia.—

One death, in 1947, was attributed to anesthesia. Certainly this should be preventable. Although it is not a common cause of fatalities with present

methods and anesthetic agents, how often do "near fatalities" occur due to the administration of anesthesia to women for delivery?

Puerperal Sepsis.—

The fact that no deaths from sepsis have occurred since 1944 might be expected with the advent of modern chemotherapy and newer antibiotics.

Summary

1. A review of thirty-eight obstetric deaths occurring in 42,559 deliveries in the years 1939 to 1948 in the City of Edmonton is presented. Twenty-one of the thirty-eight were assessed as preventable.

2. Hemorrhage and shock were the commonest causes of fatalities, accounting for 24 per cent of the total. An attempt has been made to set forth in general terms the reasons for these deaths.

3. The cesarean section rate is increasing, but in the last nine years there were no deaths in 660 sections; and, in the last two years when the cesarean rate has exceeded 2 per cent, no deaths have occurred from hemorrhage and shock or from "toxemias."

4. Coincident cardiac disease accounted for 16 per cent of the total deaths, being the third commonest single cause.

5. No deaths from puerperal sepsis have occurred since 1944.

Conclusion

In conclusion, reference is made again to the institutions concerned. Three of the four hospitals in Edmonton are open to the profession at large, and 85 per cent of the total deliveries were made in these three hospitals, and in the nursing home for unmarried girls. At risk of repetition, let us again look at the records of the fatalities due to hemorrhage and shock. Four of the total of nine occurred in one open hospital, in 11,652 deliveries, while in another open hospital over 15,000 consecutive patients have been delivered without a death from this cause. The deductions from these facts are obvious. Fortunately for us in British Columbia and Alberta, during the past two years, the Red Cross Blood Transfusion service has been of great benefit, and doubtless some lives have been saved because of this service.

In other centers the circumstances will vary greatly. In every locality the responsibility for leadership in the practice of obstetrics will fall to a considerable degree on those who are now or who will become members of this Society. It therefore behooves us to stimulate the staff of each hospital to review critically all maternal deaths, so that the members may benefit by the lessons so taught.

We must also strive for better consultation service in every hospital, and be prepared to provide that service—if necessary, free of charge—to advise and aid the general practitioner who will always deliver a large percentage of our women.

Finally, if we are to approach our goal of no maternal mortality, we must be sure that, in the teaching of students, adequate time and emphasis are placed on these serious complications.

ARTERIOLOSCLEROTIC PREGNANCY TOXEMIA*

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(From the Department of Obstetrics and Gynecology, University of Minnesota Medical School)

THE whole field of hypertensive cardiovascular disease is coming more and more to be a public health problem of the first order as knowledge of its background and its ravages increases. A wide range of special interests are involved and at least as wide a range of application may be concerned. For the obstetrician, a special series of problems is presented. These are beginning to be sorted out. Special features which detach them from or relate them to the general problem are being recognized. It is becoming clear that there is here a remote destruction rate which is greater than one would like to believe.

Two main types of hypertensive pregnancy toxemia are seen. The pre-eclampsia, eclampsia complex has been given the attention which something dramatic and immediate always commands. The less dramatic permanent proliferative arteriolar hypertensive toxemia which is to be the subject of this consideration has not been accorded the interest and study which its practical effects demand. The obstetric texts give prolonged attention to the pre-eclampsia, eclampsia group and negligible space and interest to those toxemias associated with permanent hypertension. In a twelve-month period in 1941-1942, there were 112 maternal deaths in Minnesota. Only four of these were due to eclampsia. A reasonable calculation shows that, in the same period, about 500 women died as a result of a permanent hypertension which began with a hypertensive pregnancy toxemia occurring in the previous ten years. The real relative significance thus is clear.

What is this disease? A good deal of confusion has arisen which has not been helped by the variety of terms given to it. Chronic nephritic toxemia was a misnomer and its use did a serious disservice to an understanding of the problem. It has nothing to do with chronic parenchymatous nephritis. Hypertensive vascular disease as a term means nothing or rather too much. Essential hypertension of pregnancy is better but has defects which will be discussed below.

The clinical picture is commonly familiar and needs little description here. A patient, often with a family history of hypertension, becomes pregnant and develops a hypertensive toxemia. The blood pressure and/or albuminuria may, but usually do not, return to normal at discharge. A diastolic blood pressure of more than 90 mm. Hg is present at the six weeks' return examination. The albuminuria has usually disappeared. Kidney function tests show normal results. The retinal vessels show only minor spasm. With time, this may progress or may stay relatively fixed, following the same general pattern of progression which is seen in essential hypertension without pregnancy relationship.

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It must be remembered that these obstetrical patients are likely to be relatively young and so subject to rapid progression of the disease. The shortest interval between onset and destruction with malignant nephrosclerosis which the author has observed has been two years. This is rare and the time interval is usually much longer.

If a subsequent pregnancy occurs, it is usual that in the early months there is a rise in blood pressure above the prepregnant level. One might speak of this as a functional increment since at least some of it disappears with completion of the pregnancy and since it resembles a superimposed pre-eclampsia which may be of an order to become the determining feature in treatment. When the pregnancy is concluded, the patient is usually left with a basic hypertension as measured by the average resting diastolic pressure which is somewhat higher than before this pregnancy.

This advance in the base level of hypertension as a result of an added pregnancy is not always seen. It may be absent particularly in those who have had for a long time a low level of hypertension which began with a pregnancy. Soma Weiss referred to this as hypertension uninfluenced by pregnancy. If the permanent hypertension began in a reasonably recent pregnancy toxemia and if the nonpregnant diastolic level has reached 100 mm. Hg, there are very few in whom a subsequent pregnancy does not lead to some progression of the lesion.

An essential hypertension beginning without relation to a toxemia and preferably before the first pregnancy seems to be relatively uninfluenced by pregnancy. Homer Smith states flatly that these patients may be given a good pregnancy prognosis. One such patient at the University of Minnesota Hospitals began a first pregnancy with a diastolic pressure varying about 120 mm. Hg and completed the pregnancy at term without evident change. Several similar patients with lower levels of hypertension have been observed with the same result. These, however, make up such a minute fraction of the total that they do not change the basic conclusion as described above. It does strongly suggest that there is a significant difference between the mechanism of essential hypertension and that of this pregnancy-induced lesion.

Once established, the permanent hypertension may take a variety of courses. This can be expressed only by the vague statement that there is considerable variation in the inherent potential for progress in the individual patient. Not only does the inherent potential vary from individual to individual but it varies as between one organ system and another in the single patient. Usually the vessels of kidney and central nervous system show most marked change but occasionally these may be outstripped by changes in the vessels of gut, pancreas, or adrenal. In addition, the prognosis is more favorable in those who do not become hypertensive until the later years of the reproductive period; in those in whom the disease has been present for a considerable time without too marked advance; in those who are not obese or who will control their obesity; and particularly in those who can be gotten past the menopause with diastolic pressures at rest well below 110 mm. Hg. In this last group, the prognosis is much more

favorable than in men with the related essential hypertension of similar degrees of advance. It is to a considerable extent in this fact that the hope of surgical and dietary interference for women lies.

In some, then, the disease may be relatively benign. In others, particularly where repeated pregnancies have exerted a deleterious effect, the progress of the disease may be rapid. The hypertension increases, the left side of the heart dilates, and the proliferative lesions in the retinal vessels progress. Suddenly, the patient begins to complain of visual disturbances, shortness of breath and palpitation, headaches, and general weakness. Urine output decreases and may contain blood. Blood urea nitrogen rises. This may be called renal decompensation in fairly strict analogy with the changes of cardiac decompensation. Uremia develops and the patient dies of cardiac and kidney failure. Only occasionally does cerebral hemorrhage cause death.

In order to study these lesions, the autopsy material at Johns Hopkins Hospital was used. This is not the place to go into histologic details. Reference is made to the report by McKelvey and McMahon.[1] In brief, in those patients who died of other disease after the previous establishment of a permanent hypertension following a pregnancy toxemia, vascular lesions were found in the arterioles of kidney, central nervous system, adrenal gland, and pancreas and were those described by Volhard and Fahr as benign nephrosclerosis. If the patient died of uremia after the characteristic clinical events as described above, an acute process was added to the chronic proliferative lesion. The small arterioles, particularly in the kidney, had now given way as a result of the passage further and further down the more and more damaged arteriolar tree of the peripheral resistance to increasing systemic pressures. This finally reaches an intolerable degree when the distal arterioles give way allowing the escape of blood and plasma. The kidney is now decompensated and uremia ensues. These are the lesions described by Volhard and Fahr as malignant nephrosclerosis and studied in detail by Schurman and McMahon.

One cannot distinguish morphologically between the vascular lesions of the result of this type of pregnancy hypertensive toxemia and that described as nephrosclerosis or essential hypertension in the nulliparous woman or the man. There seem to be evidences of a demonstrable functional difference in the degree of resistance at the afferent and efferent arteriole to and from the glomerulus, although our own studies would leave this somewhat vague. Reference is made to the work of Corcoran and Paige, Homer Smith and his associates, and others. That there does seem to be a clinical difference has already been discussed.

The point to be made is that what is found here is a proliferative sclerotic lesion of arterioles with widely spread manifestations. It is, then, an arteriolosclerosis and it is recommended that for the sake of accuracy and understanding, the condition be referred to as arteriolosclerotic pregnancy toxemia.

Now, what is its significance? Stander and Peckham showed long ago, using the Johns Hopkins material, that 40 per cent of the hypertensive toxemias of pregnancy either began or ended up as this condition which they called chronic nephritic toxemia. For those who had no further pregnancies after

the diagnosis was established, there was found a 20 per cent ten-year mortality attributable to the disease. If one or more pregnancies followed the diagnosis, the ten-year mortality rose to 40 per cent attributable to the arteriolosclerosis. This has been almost exactly repeated in a smaller Minnesota series and it has been confirmed by other observers as well.

One can now make some calculations designed to try to arrive at the relative significance of this condition. But it must first be agreed that the obstetrician must more and more project the basis for the evaluation of his decisions into the remote future. Surely this needs no great effort at persuasion of those who are dealing with malignant disease, hepatitis, birth injury, rheumatic heart disease, and dozens of other such problems. The time has gone when one can be satisfied when a patient has left the hospital alive. One must also aim at knowledge and control of the future.

There is too wide a range in the reported incidence of hypertensive toxemias to allow any very accurate conclusion to be drawn as to the unselected incidence. No closed community study has yet been reported. But it seems fair to assume that about 5 per cent of pregnancies will be hypertensive. Forty per cent of these will be arteriolosclerotic or 2 per cent of pregnancies. The death rate (20 to 40 per cent) in the subsequent ten years would lead to the conclusion that between 0.4 per cent and 0.8 per cent of pregnancies will be paid for in the future by destruction from arteriolosclerosis alone. Minnesota has had a maternal death rate in the past two years of 6 and 6.6 to 10,000 live births or 0.06 per cent. There are statistical inaccuracies in the calculation of the arteriolosclerotic death rate but these are more than compensated for by the grossness of the difference. The conclusion seems clear that arteriolosclerotic pregnancy toxemia alone is causing many times the destruction rate of all the other immediate causes of maternal mortality. Here, then, is our urgent obstetrical problem.

What can be done about it? Unfortunately, fundamental knowledge of hypertension is lacking so that the tools at hand are at best second rate. But some practical things can be accomplished even though they leave much to be desired in terms of complete effectiveness.

The first problem is recognition of the lesion. The details of this are common knowledge and the only difficulty is to get them applied. There is no one who cannot take a history and blood pressure measurements, look at the retinal vessels, and do an adequate six weeks postpartum examination. Recognition is most often as simple as that. Other causes of hypertension can readily be ruled out.

One must learn to try to avoid wherever possible prolonging the hypertension of pre-eclampsia, particularly when this is of severe degree. Chesley and others have demonstrated beyond reasonable doubt that the duration of such hypertension is directly related to the frequency of this form of arteriolosclerosis.

It is clear that pregnancy added to an established arteriolosclerotic toxemia, particularly when nonpregnant diastolic pressures of 100 mm. Hg or above have

been established, may be expected seriously to speed up the progress of the vascular disease. It is wiser for such women not to undertake a subsequent pregnancy. If the nonpregnant diastolic pressure at rest is 110 mm. Hg or more, progress of the disease is reasonably certain and the chance of the production of a viable child is small. Therapeutic abortion is occasionally clearly indicated although efficient prevention of pregnancy is much more desirable.

The present hope of really efficient treatment for a large group of these patients lies in weight reduction, sodium restriction, and sympathectomy. There is too little experience as yet with this particular form of hypertension to justify dogmatic conclusions. Blood pressure can be reduced but real evidence of significant prolongation of life is still to be obtained. Remarkable reports are in the literature of uneventful pregnancies following sympathectomy in well-established severe lesions.

In the absence of a proved basis for establishment of a policy, the Department of Obstetrics and Gynecology at the University of Minnesota is treating those patients with nonpregnant diastolic pressures at rest below 100 mm. Hg by conservative means and observation. Procedures are taken to see that they do not become pregnant. In those with diastolic pressures above 110 mm. Hg and particularly where the vascular lesion can be demonstrated to have a major spastic component, sympathectomy is the method of choice. Sympathectomy has not been done during pregnancy but this has been occasionally reported and might be done on special indications.

Insufficient time has elapsed to allow an evaluation of the results of sympathectomy. There has been an irregularity of apparent results which leaves one disinclined to consider it a final solution to the problem. It is, however, promising, and in the presence of severe lesions may be the only reasonably hopeful approach.

Here, then, is the problem. Much more can be done than is being done at present to combat it. It is the hope of all concerned that the future will bring more basic knowledge and more effective therapeutic tools. In the meantime, there must be an increase in the efficiency of the use of what is available.

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Discussion

DR. GEORGE B. MAUGHAN, Montreal, Quebec.—Dr. McKelvey has given us a panoramic view of a problem that confronts each of us infrequently, but which, on its appearance, calls for our best exercise of judgment. I am sure all feel as I do that the mortality rate from postpregnancy hypertension—over 100 times that from eclampsia—is truly startling. One wonders if we are doing our duty as curators of maternal health when such statistics exist. Perhaps we should review our attitude and our judgment, and renew our efforts toward successful treatment of this disease.

We have heard that arteriolosclerotic pregnancy toxemia is a disease, which by its very nature affects all organs of the body. Many old concepts die hard and one of these with the greatest artificial longevity is the concept of toxemia of pregnancy as a "kidney

disease.'' Much research has been wasted on this idea. A year ago I presented evidence of liver damage in toxemia and at that time showed the greatest incidence (75 per cent) in renal disease complicating pregnancy. Further work has brought this latter figure into line with other toxemias. Now we find that between 30 per cent and 50 per cent of all toxemias of pregnancy show liver damage demonstrable by the cephalin-cholesterol flocculation test. This, however, is but another manifestation in another parenchymatous organ of the widespread devastation, temporary or permanent, in the body afflicted with toxemia. The etiological factor still eludes us and, until we find it, prophylaxis and treatment must necessarily be groping and symptomatic.

Dr. McKelvey has been unfortunate enough to have under his care many cases of arteriolosclerotic toxemia of a severity we seldom see in Montreal. Admittedly our follow-up cannot compare with the speaker's, but in our experience it is very rare to find a diastolic blood pressure of 100 mm. Hg or over in the first two or three years post partum. There may be a dietary factor in this difference and I am convinced that further accurate research into this aspect of the problem may uncover some much-needed basic information. Until such time as we have this basic knowledge, we must accept and use such second-best methods of prevention and treatment as outlined by Dr. McKelvey.

One of the most severe psychic blows one can inflict on most women is to terminate their ability to reproduce, and yet, in arteriolosclerotic toxemia, what other choice is left? In the best conservative tradition our experience with sympathectomy is quite limited. Our legal advisers at the Royal Victoria Hospital have ruled for us that interruption of pregnancy is justifiable only if the child must be sacrificed to save the mother's life. How far into the future can we honestly project this concept? My personal conviction agrees with the oft-expressed opinion of the laity—''better a live mother of one or two than a dead mother of three.'' Once the diagnosis of arteriolosclerotic toxemia is established, I believe it is infinitely preferable to prevent pregnancy than to interrupt it. If four to eight of every 1,000 mothers are slated to die of the aftereffects of pregnancy within ten years, let us bend every research effort to find the proper prophylaxis against arteriolosclerotic toxemia, but, while we cannot now prevent the toxemia, let us shed our hypocrisy and prevent the pregnancy. Or when the pregnancy is presented to us as a *fait accompli* let us interrupt it and prevent all future pregnancies by ligation of the tubes. In our present state of knowledge can we do less and still hold ourselves in high regard as curators of maternal health?

CONTRIBUTION TO THE STUDY OF THE ETIOLOGY AND PREVENTION OF CANCER OF THE CERVIX OF THE UTERUS*

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THE aim and object of this presentation is the hope of broadening our knowledge concerning one of the factors long suspected of carcinogenetic action, affirmed by some and denied by others, and to show that prevention of carcinoma of the cervix is possible if the presence of this factor is really essential to its appearance and development.

Almost all publications mention the possibility that cervicitis is a basic cause of carcinoma of the cervix of the uterus.

Richard Te Linde, while agreeing with the opinion held by a number of gynecologists, based on actual clinical experience, namely, that chronic inflammation of the cervix predisposes to the development of cancer, declares textually: "No one has ever proven conclusively that cervical lacerations and cervicitis predispose to the development of carcinoma."[1]

Norman Miller states: "While the causation of cancer of the cervix is unknown, much has been written concerning the common benign lesions of the cervix and cancer. Covincing evidence of such relationship is lacking, but even so the correction of all common cervical lesions is indicated on the grounds that cancer does not commonly appear in a healthy organ."[2]

Clinicians have reported the results of treatment of cervicitis and its relation to the development of carcinoma of the cervix. Craig writes that he did not observe a single case of cancer during a period of ten years and over in the 2,895 cases of cervicitis which he treated and cured.[3] Pemberton and Smith affirm that they did not discover a single case of cancer among the 1,408 women whom they treated for and cured of chronic cervicitis. This is equally true of another 740 women on whom was performed an amputation of the cervix.[4] Karnaky reports that at Jefferson Davis Hospital, where 5,000 women underwent conization, not one case of cancer was observed.[5]

On the other hand, Schiller and other authors have expressed the opinion that cervicitis, far from being the cause of the development of cancer, would, on the contrary, be but secondary to its appearance.[6]

Novak declares: "There is still considerable difference of opinion among gynecologists as to the importance or unimportance of chronic cervical irritative lesions as predisposers to cancer and Miller has recently published a study in which this danger is minimized." And he adds, "Cancer can develop in cervices in which no evidence of previous chronic irritation can be demonstrated. In my own experience I have, as a matter of fact, been impressed with the fact that a considerable proportion of the early cancers which I have seen have been noted in cervices showing no noticeable evidence of previous chronic inflammation or irritation."[7]

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In the presence of divergent, even contradictory opinions on the subject, it is not surprising that too often the treatment of cervicitis as a preventive measure be advised in listless, almost academic fashion, when it is perhaps of vital importance that it be advocated and generalized at all costs.

Two important questions therefore arise. The first is how to convince doctors, who do not specialize nor have any particular interest in gynecology, that they should not tolerate the presence of cervicitis among their patients. The second, how to launch a major educational campaign when many theories oppose one another and so much obscurity on the subject still exists.

Under these circumstances, it is absolutely necessary that the proof be established that cervicitis is one of the essential factors in the development of this cancer, if so it be. That is the crucial point, the key to the solution of the problem.

As previously stated, for some time gynecologists have remarked that they found no cancer among women who had been treated and cured of cervicitis. However, reports of observations of cancer developed in women so treated have or will be published. It would be difficult to imagine that all these patients were completely cured or that they never again will be exposed to the usual causes of cervicitis.

This approach to a vital problem would result only in endless discussions which would bring about the great disadvantage of delaying its solution. This is due to the fact that the preventive effects of such treatment cannot be judged until every patient has reached the age of at least 65 years, or until death has occurred. The proof could hardly come from this source. Because too many years of observation would be necessary before sufficient certainty could be acquired, it was decided to carry out the research work in another direction.

If, in reality, cervicitis is the basis of the cancer of the cervix, this cancer should not exist among women whose social state and mode of life protect them from the usual causes of cervicitis or chronic irritative lesions, namely nuns.

As a gynecologist, I have had, over a long period of years, the advantage of observing and studying a numerically important group of women living in the above-mentioned social state. This conviction gradually grew that this variety of cancer did not exist among them, or that, if it did, it existed only in very exceptional cases. To make sure that this was not an isolated fact, extensive research work in a number of similar groups dispersed over a wide area was carried out.

Purposely, unmarried women living in the ordinary outside world were omitted for research purposes, for reasons which it is not necessary to mention.

The investigation was concentrated exclusively on carcinoma of the cervix uteri and of the corpus uteri, the latter serving as basis of comparison.

A survey of the medical files of an annual average of 13,000 women, covering a twenty-year period, was carried out in the archives of many different convents of nuns. This figure of 13,000 adult women represents, in civilian life, a city with an unchanging population of approximately 65,000 inhabitants, calculation based on the last census taken in Canada.

This research, to be sure, covers a still longer period of time and a much wider range of subjects. Several of the groups concerned, as a matter of fact, furnished statistics extending over periods of 25, 30, 40, 60, and even 86 years, but these figures were not used despite the fact that the causes of death had been carefully recorded. Pathological reports evidently are absent, incomplete, or obscured by too great a possibility of error, over such a long period of time and dating so far back.

Although I had the privilege of consulting the medical files, compiled and well kept by the attendant physician of a convent for fifteen years, statistics covering a group of some 1,500 women were set aside because, after their deaths, their files at the convent are destroyed.

In the case of another group, about 2,000 women, it was also preferred not to use the information regarding them because the data, gathered from their Mother House over a period of twenty years, could not be verified completely. The reason for this was that the pathological reports of the district hospitals, where they had been treated were not complete, although only a small fraction of these cases were not the subject of investigation.

The comparative frequency of carcinoma of the cervix uteri and the corpus uteri, according to the statistics of different authors, varies between 8 and 5 of the former for every single one of the latter. This proportion, according to Novak, is 7 to 1; to Meigs, 6.2 to 1; and to Norris and Vogt 5.6 to 1.[8]

Material

In Table I are given the results of the research work carried out in the previously mentioned group.

TABLE I. ANNUAL AVERAGE, 13,000 WOMEN. PERIOD OF TIME, 20 YEARS

CARCINOMA OF CORPUS UTERI		CARCINOMA OF CERVIX UTERI
Histologically confirmed	12	-
Diagnosed in the course of operation	1	-
Diagnosed clinically	1	-
Total	14	-

By taking Meigs' index of frequency, 6 to 1, with 12 cases of cancer of the corpus uteri histologically confirmed, 72 cases of carcinoma of the cervix should have been found, but, I repeat, not a single one was discovered. The inverse ratio of frequency is evident in these statistical data.

The results in the groups set aside are identical to those which have just been given. If they were omitted, it was because the inquiries could cover only a period of fifteen years in one case, or could not be completed in the other.

It seems difficult to ignore the mathematical strength and power of these figures. To do so, it would be necessary to assume that the medical statistics on the subject, widely accepted and used for at least the past twenty years, were entirely wrong. This would mean that, if error there be, such statistics should have maintained that cancer of the corpus uteri is more frequent than cancer of the cervix uteri.

This would mean, too, that based on these results, in a city with an unchanging population of about 65,000 inhabitants, there would not have been a single case of carcinoma of the cervix uteri during a period of 20 years.

Intrigued by these observations, stupefied, not to say alarmed, it was decided to study and attack the problem from another angle. A survey of the archives of pathological laboratories and radium treatment centers was made, forgetting the archives of the convents which had heretofore been consulted.

The object in doing this was to verify, over a vast area in which there existed numerous identical groups but in which sphere no investigation had been made, whether or not the findings would contradict or confirm the results perviously obtained. It was expedient to do this because the area was much too vast and the identical groups too numerous to be visited individually.

I therefore made a survey of the pathological archives of malignant tumors of the uterus in laboratories of two large hospitals in Montreal and also in the pathological diagnostic centers serving the hospitals of approximately the eastern two-thirds of the Province of Quebec, the Magdalen Islands, the French Islands of St. Pierre and Miquelon, and a few hospitals in New Brunswick. The statistical work in this connection covered periods of time varying from twelve to twenty years.

The archives of treatments given at Montreal's Radium Institute for the past twenty years and those of the Radium Institute of Quebec, since the latter's foundation twelve years ago, were the object of investigation.

Evidently, a large number of anatomical specimens which do not present any special diagnostic difficulties are not sent to diagnostic centers due to the considerable distance which exists between the latter and the various regional hospitals concerned. It is also likely that anatomical specimens are sent to laboratories in the metropolis not searched in the course of this investigation.

It is evident, of course, that a few of the tumors, once discovered in convents' archives by the first method of investigation, are duplicated among those found in the archives of pathological diagnostic centers where the anatomical specimens from these convents are sent for diagnosis.

Once again, would this research in hospital laboratories corroborate or come into conflict with the facts found in the archives of convents?

The verification of pathological reports resulted in the reclassification of two malignant tumors of the cervix uteri in the category of cancer of the corpus uteri. Actually, they were but the propagation of cancer of the corpus uteri to the cervix.

Results

After taking these changes into consideration, the results obtained by the second method of investigation on malignant tumors found in nuns are shown in Table II.

TABLE II

CARCINOMA OF THE CORPUS UTERI		CARCINOMA OF THE CERVIX UTERI	
Histologically confirmed	19	Histologically confirmed	3
Total	19		3

With the 6 to 1 ratio frequency, 114 cases of carcinoma of the cervix should have been discovered.

There is no necessity to comment on the surprising similarity of the results obtained by the research work carried out from two different angles.

It is possible, either inadvertently or as the result of clerical error, that a few cases of carcinoma of the cervix may have escaped attention. About 140,000 odd unclassified pathological reports were the object of survey in addition to those that were classified. There is certainly room for error.

However, the striking similarity of the data obtained by the two different methods of research leads one to believe that the errors, if any, would be so rare that they could in no way change the significance of the results.

Research work on such a large scale, covering so long a period of time, can hardly be done with absolute mathematical precision. It was therefore deemed advisable to narrow the field, but only to the extent the results obtained would be equally indicative and where, as far as possible, every nook and corner would be explored, namely, archives of the convents concerned, archives of pathological laboratories, and death certificates. In the course of this third investigation, a related study of cancer of all organs would now be made in relation to carcinoma of the cervix.

It is relatively easy to diagnose cancer of the breast and of the body and cervix of the uterus on account of their accessibility but it is much more difficult to do so with deep cancers. Because of this difficulty, it was necessary to choose carefully, with regard to medical supervision, the groups to be investigated. Each convent selected for special study is attended by a different staff of physicians, surgeons, and specialists, most of them university professors. The margin of error in diagnosis should therefore be acceptable.

This last investigation covered a yearly average of 3,280 nuns over a period of twenty years. This number of 3,280 nuns is the population of four different Religious Orders or four groups of convents of nuns. This number of adult women would represent in civilian life a city of an unchanging population of about 16,000 inhabitants. Results are shown in Table III.

TABLE III. MALIGNANT TUMORS OF ALL ORGANS
ANNUAL AVERAGE, 3,280 WOMEN. PERIOD OF TIME, 20 YEARS

Skin	3
Thyroid gland	1
Skeleton	1
Spleen	1
Urinary tract	5
Buccal cavity	3
Parotid gland	2
Greater omentum	1
Mesentery	1
Digestive tract	42
Liver	4
Pancreas	2
Breast	53
Ovary	9
Corpus uteri	2
Cervix uteri	0
Malignant tumors of all organs	130
Carcinoma of the cervix uteri	0

For several years, I have been in charge of Group I as gynecologist and have been in a particularly favorable position to study this group. The diagnosis of carcinoma of the corpus uteri observed in this group was first made clinically, then by exploratory curettage, and histopathologic examination. The two patients were operated upon and the diagnosis confirmed by macroscopic and histologic examination of the organ removed in the course of the surgical operation.

Since no carcinoma of the corpus uteri was observed in Groups II, III, and IV, there is practically no likelihood of misinterpretation. Consequently, there are 130 malignant tumors of various organs on one hand and not a single one of carcinoma of the cervix uteri on the other.

Once again one might be amazed that in a city with an unchanging population of some 16,000 inhabitants over a period of twenty years, not a single case of carcinoma of the cervix would be observed. Then, why is it that cancer which strikes so savagely everywhere else in the human body stops short before the cervix of the uterus in these women?

Comment

What conclusions may one draw from these facts? In the field of cancer research, theories have given rise to so many disappointments that one must be prudent in the interpretation of facts. However, the significance of those submitted can hardly be overlooked.

In comparing two groups of women living in different social conditions, one frequently exposed to the cause of cervicitis and the other only exceptionally so, the immense importance of chronic cervicitis in the genesis of carcinoma of the cervix is clearly pointed out, and this, without denying or minimizing the roles of heredity, acquired constitutional states, viruses, enzymes, deficiencies, and of biochemical and hormonal influences.

Ayre published recently an interesting study in which he claimed that vitamin B deficiency, thiamin and possibly riboflavin, in association with a local excess of estrogens and cervicitis, may indirectly cause carcinoma of the cervix. Since then, a few authors have done research work on the same subject.

It is commonly accepted that prolonged excessive estrogen stimulation causes hyperplasia of the endometrium. However, they have remarked that the hyperplasia of the endometrium was found only in a very few cases though it should frequently exist if really there is a prolonged stimulation by excessive estrogens due to vitamin B deficiency. So, if that is true, the importance of cervicitis may be still greater because probably the facts observed by Ayre would be secondary only.[9]

It is true, however, that in very rare cases carcinoma of the cervix may be found in a virgin. How can one then reconcile this clinical fact with the hypothesis that cervicitis constitutes one of the essential factors in the development of carcinoma of the cervix?

It is necessary in my opinion that, very exceptionally at least, this variety of cancer be found in virgin women. Otherwise, the previously mentioned facts might well serve to combat the theory of the carcinogenetic action of cervicitis. Authentic chronic cervicitis, most particularly inflammatory erosion, exists in virgin women even if this trouble is rare and pathological modifications superficial. This is a clinical truth observed by the attendant gynecologists of convents.

Consequently, it would be surprising were cancer never to develop in these women, if one accepts the premise that cervicitis really has carcinogenetic action.

Furthermore, from these statistical surveys it appears that, as far as the uterus is concerned, there exists no sole cause of cancer. Different factors are involved according to whether or not it is the corpus or the cervix which is affected.

If cervicitis is a necessary etiological agent, an obligatory one, its cure, theoretically, should also bring about the disappearance of cancer of the cervix. The clinical results brought forth by Douglas, Karnaky and Pemberton and Smith seem to confirm these theoretical views.

May I be permitted to add that in well over 4,000 cases of cervicitis, treated systematically during the last 17 years, both at the hospital and in private practice, I have not yet come across a single carcinoma of the cervix. For the past

decade, I have taught that the eradication of cervicitis equals the suppression of cancer and, up until now, not one single observation of carcinoma has been brought to my notice which would contradict such assertion.

"No one has ever proven conclusively that cervicitis predisposes to the development of carcinoma," says Richard Te Linde, previously quoted in this respect. At the risk of being accused of presumption, I believe that the results of this research may furnish a link leading to this long-needed proof.

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Discussion

DR. JOHN L. McKELVEY, Minneapolis, Minn. (By invitation).—Dr. Gagnon has presented a most intriguing study. He has controlled his material to the very best of his ability and has satisfied himself that there are no artificial factors of selection. Under these circumstances, it is strongly suggested that here is significant information which must be given consideration in any discussion of the etiology of carcinoma of the cervix. That it will be a cause for much argument is clear.

The data presented in the paper should be considered separately from the conclusions. Dr. Gagnon has demonstrated that, so far as he can determine, the incidence of carcinoma of the cervix in nuns is negligible. That in itself is a startling finding. It is a long jump to the conclusion that this is due to a lack of the common inflammatory lesions of the cervix and obvious objections will be raised to the whole-hearted acceptance of this. Among these is the hard fact that no one has yet demonstrated the transitional stages between erosion healing and cancer. Nor does it explain the absence of squamous-cell carcinoma of the cervix in Jewish women.

The simple findings presented by Dr. Gagnon are important. Studies designed to confirm these findings must be quickly undertaken. If this proves to be generally applicable, it can change and to a certain extent direct the line of attack upon this confused problem of etiology.

DR. MAUGHAN, Montreal, Quebec.—I regard this as an extremely important piece of work, and something that has not been investigated before. It is most unusual to have available for study such a very large number of women as in Dr. Gagnon's series. After listening to Dr. Gagnon in Quebec, two years ago, indicating that these results would probably be found, I have urged more strongly than ever the care of the postpartum cervix.

I wish to urge on all our obstetricians and gynecologists to take better care of the cervix immediately after the third stage and later six weeks to three months post partum. Personally, I cauterize almost 100 per cent of cervices six weeks post partum, and repair immediately after the third stage all lacerations over 1 cm. or so in length. I do not yet know if it means anything in the prevention of cervical cancer, but I do believe that obstetricians are much too careless about the care of the cervix.

IRREGULAR SHEDDING OF THE ENDOMETRIUM*

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THOSE who deal with the clinical problems of abnormal uterine bleeding will have no difficulty in agreeing with the statement that there is much yet to learn in this field. To use such terms as functional bleeding and menometrorrhagia to describe a given clinical or histological picture is only to say that it is not understood. Gradually, however, it is becoming possible to sort out the various conditions which give rise to abnormal uterine bleeding. With the exception of those bleedings due to specific blood dyscrasias, the tools which are opening the field to objective approach are those of careful histological control and quantitative endocrine determination. A relatively new arrival is this entity to which German investigators have given the term irregular shedding of the endometrium. It is the purpose of this presentation to define the condition, to attempt to justify its acceptance as a specific pathologic entity, to describe work which has been done at the University of Minnesota and which is aimed at clarifying its etiology, and to discuss some of the problems of its recognition and treatment.

Irregular shedding of the endometrium is a condition in which there is a prolongation of the normal processes of shrinking, shedding, involution, and finally epithelization of what has been secretion-phase endometrium. As such it is a menorrhagia and may be expected to have nothing in common with the various metrorrhagias from a histological, etiological, or clinical point of view. It shares with these only the one clinical feature of uterine bleeding. In irregular shedding there is seen a prolongation of menstruation with various degrees of profuseness of the blood loss. Occasional patients may bleed for twenty days of a more or less regular twenty-eight day cycle. The more usual duration is seven to twelve days. Blood loss may be sufficient to produce a severe anemia. Study of this shows it to be of the secondary or iron deficiency anemia type with high protoporphyrin values, high serum iron combining capacity, and presumed severe depletion of iron stores, but with no interference with the capillary or blood mechanisms of hemostasis or clotting. There is some interference with the tempo of the menstrual cycle but it is usually minor and a careful history will usually make clear the fact that it is a disturbance of menstruation as such.

What is this condition? There is no evidence to suggest a disturbance of blood clotting mechanisms and sufficient numbers of uteri are now available for careful complete examination to rule out any gross lesion as a cause of the bleed-

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ing. It will be necessary then to inquire into the histological details of the disturbed endometrium itself and to investigate carefully the steroid endocrine status at least in the second half of the cycle.

The key to the recognition of the histological features which characterize irregular shedding lies in the knowledge that this is a self-limited process. At the very beginning of the bleeding, the endometrium is almost indistinguishable from that of early menstruation. In the nonbleeding phase, there is no certain distinguishing feature. All stages between these may be seen and the histological characteristics will be largely determined by the proportion of that particular bleeding phase which has passed when the endometrium is taken. In general, the microscopic diagnosis is most easily made by comparing the findings in a given section with what should be present in the normal for that day of the bleeding. The clinician, then, must do two things. He must choose the day of the curettage to satisfy the histologist's problem. Thus, a patient who is expected to bleed for eight to ten days is curetted on the fifth to seventh day. Second, he must supply this information to the histologist who must use it.

There are four processes which go on in menstruating endometrium and which may be recognized as variously disturbed in irregular shedding. They are interdependent in the sense that they follow one another more or less in order as given and in that the last phase, wound healing, will not occur until the others are at least nearly complete. These have been described in detail by Van Dyke, Markee, Bartelmez, and others. The first is shrinkage by which both extracellular and intracellular water is lost by the stroma cells. This begins well before the onset of bleeding and apparently follows quickly and easily on the withdrawal of progesterone. Indeed, it seems to occur at a higher level of progesterone in process of gradual withdrawal than do the later events. Thus, incompleteness of this process is less evident in irregular shedding than incompleteness of the later events.

There has been much argument about the second of these processes, endometrial shedding. Robert Schröder thought of this as being rapid and complete. It is now known that the lower uterine segment endometrium sheds poorly and endometrium about the tubal opening sheds late. The main endometrium does not necessarily shed completely, particularly that which is close to the large coiled arterioles. Various degrees of retention of endometrium which has functioned may normally be retained to undergo the third process, namely that of involution or return to the status quo ante. Thus endometrium, both glands and stroma, which has undergone response to progesterone effect may return to the less differentiated proliferation-phase state and take part in a subsequent cycle. This, of course, would have to occur in the pregnant uterus where both basalis and functionalis undergo complete change to secretion-phase type. In irregular shedding, abnormal degrees of retention of endometrium of the functionalis occur.

In the normal cycle, the third process, involution, is ordinarily a minor problem. There is little functionalis to involute and what there is is usually close to the basalis. In the absence of progesterone in even subthreshold quantities, shedding and involution of what is retained proceed smoothly and quickly.

In irregular shedding, shedding and involution are grossly slow, incomplete, and irregular. They are slow, in that the process lasts for an abnormal time, usually to about ten days but sometimes longer. They are incomplete in that a grossly abnormal amount of secretion-phase changed endometrium is retained, particularly about the large vessels. They are irregular in that all stages of involution with various degrees of retained secretion-phase change may be seen scattered through a single endometrium. This gives at once a microscopic picture of gross irregularity from which the condition received its name from Robert Meyer and his pupils.

The fourth process, healing, involves the completion of epithelization of the endometrium. It will not occur until the previous three processes are well advanced. Bleeding continues until healing has occurred since an open wound persists to this time. There are further factors in this bleeding of irregular shedding but not enough is known of them at present to justify discussion. Ordinarily, wound healing occurs on the fourth to sixth day of menstruation. Robert Schröder has shown pretty pictures of this. The curetted material of irregular shedding will show no surface epithelium until just before the spontaneous end of the process. This is one of the hallmarks of irregular shedding.

The characteristic clinical picture is that of a patient usually in the 30- to 40-year age group who has gradually developed profuse and prolonged menstrual flow. It may start suddenly with the re-establishment of menses post partum or post abortum. The cycles may come at slightly prolonged intervals but usually approximate the normal experience and are sufficiently regular to justify the assumption that the disturbance is one of menstruation as such, a menorrhagia. It is unusual that the bleeding lasts beyond twelve days although one patient bled for twenty-one days of an approximate thirty-two-day cycle. Study will rule out primary hemorrhagic disease and general physical and pelvic examination is normal.

Curettage on the fifth to eighth day of the bleeding will show no polyps, irregularity of the cavity, or evidence of malignant disease. A moderate amount of endometrium is obtained. Microscopic examination will yield findings which will vary in degree with the relative time within that patient's bleeding that the endometrium was taken.

The microscopic picture is one of an irregular endometrium which does not fit into any normal phase of the cycle. No surface epithelium is seen. Abnormally large quantities of endometrium are present. Most or all of the stroma is contracted and cellular. Occasional areas of large pseudodecidual cells may be present in the neighborhood of blood vessels. The glands are usually collapsed and sometimes star shaped. Sometimes the stroma is contracted about these collapsed glands to form little islands of scarring. The epithelium of the glands shows various degrees of secretion-phase change while many have returned to more or less normal proliferation-phase characteristics. There often appears to be an abnormal number of spiral arterioles which suggests that the endometrium farthest from the vessels has been more effectively shed. The vessels themselves have open lumina and thick, well-developed walls which suggest their abnormal retention in the functionalis for more than one cycle. In-

flammatory cells secondary to the prolonged bleeding and tissue necrosis are present but are secondary to the bleeding since they are similarly seen in the endometrium in any prolonged uterine bleeding. The whole process is not necessarily similarly advanced in all areas. The degree of the changes is relative to the time within this self-limited process at which the endometrium is obtained.

This is an abnormal endometrial pattern. It is characteristically associated with various abnormal degrees of profuseness and prolongation of menstrual bleeding. The normal endometrium should show a clearly different picture at this time. There is no other associated abnormal condition in the uterus. It appears to be a histological entity. It is not an uncommon clinical entity.

Etiology

A variety of suggestions have been made as to the nature of the endocrine disturbance responsible for irregular shedding of the endometrium. Most of these were based on single-specimen or short-term assay. A group of these patients were studied using total urine excretion over at least a full cycle. Estrogens were biologically assayed. Pregnanediol was determined by the methods of Venning and Brown. The results have been reported by McKelvey and Samuels. No abnormality was found in estrogen excretion. With one exception, every patient who showed the histological picture of irregular shedding also showed a persistence of pregnanediol excretion after the onset of the bleeding. This has not occurred in any other condition than irregular shedding except after the artificial administration of progesterone or pituitary gonadotropes. The one exception in our series was a patient who was curetted for diagnosis and studied through the subsequent month. Pregnanediol excretion stopped before the onset of the next bleeding but this menstrual period turned out to be normal.

E. G. Holmstrom has been able to reproduce the histological lesion in the endometrium of the human being by administering progesterone during the last portion of the cycle and early menstruation.

There is still some uncertainty as to the interpretation of the results of the presently available techniques for the recovery and measurement of pregnanediol. It would seem that the best information available suggests that irregular shedding of the endometrium is due to an abnormal duration of progesterone effect in a subthreshold quantity. It is insufficient to prolong the cycle significantly and preserve the endometrium but sufficient to interfere with normal shrinkage, shedding, involution, and healing. It thus appears to be an endocrinological as well as a histological entity.

Treatment

No specific therapy is available at present. Studies are being carried out at present, but are incomplete. Curettage is necessary for diagnosis and in this condition as in some others is frequently curative. Somewhere between one-third and one-half of these patients respond to thorough curettage. In the remainder, one has to consider the age and reproductive history of the patient and the degree of the bleeding and resulting anemia. Once the cause of the

bleeding is established and can be demonstrated to be devoid of remote danger, many patients with minor degrees of duration and quantity of blood loss will prefer to put up with the complaint. In these near the menopause, x-ray sterilization may be used. Occasionally in younger patients with severe and much-prolonged bleeding which does not respond to repeated curettage or to anything else, hysterectomy will be a necessary choice.

This is all therapy of second choice since it is not specific. Further study is required.

Conclusions

1. Irregular shedding of the endometrium is a histological and endocrinological entity associated with a disturbance of the normal processes of endometrial shrinking, shedding, involution, and healing.

2. It is one cause of menorrhagia and can be diagnosed only by properly timed histological study of endometrium obtained at curettage.

Discussion

DR. M. C. WATSON, Toronto, Ont.—Dr. McKelvey's suggestion that many of the classical terms heretofore used in the textbooks in connection with descriptions of symptoms and various phases of menstruation and uterine bleeding convey very little meaning and should be discarded should meet with general agreement.

In this connection, is not "anovulatory bleeding" an anomalous term, because of the fact that simple extrusion of an ovum from the ovary is only one function of the ovary and the relation of ovulation to the uterine response to follicular development is not at all constant? Ovulation may be accompanied by midmenstrual bleeding but in health it is more frequently not accompanied by bleeding which may or may not occur two weeks later. Ovulation may occur during periods of prolonged bleeding; during prolonged periods of amenorrhea; during late childhood; before the menarche; or even during pregnancy. It would seem to me that the understanding of future studies of functional uterine bleeding will be hindered by the use of the term "anovulatory bleeding." One might quite as intelligently speak of "ovulatory amenorrhea."

Even the term "corpus luteum" might well, in the future, be limited to the designation of that active well-formed organ in the formation of which chorionic gonadotropins play a part, as against the matured state of a follicle during normal menstruation. It is my impression that even follicles from which an ovum has been expelled do not all arrive at that final state of maturity.

That the phase of follicular maturity in the ovary and the phase of endometrial maturity should always be considered in connection with the general physical and particularly the nutritional state of the patient was correctly emphasized.

In the Toronto clinic a definite distinction is made between uterine bleeding from an atrophic or proliferative endometrium under prolonged estrone effect, in which case the resultant uterine bleeding is liable to be continuous over months or weeks thus reducing the hemoglobin gradually. On the other hand, in the endometrium in the secretory or functional phase under progestin influence the uterine bleeding is of the nature of a hemorrhage and reduces the hemoglobin suddenly. Such a distinction was claimed to be necessary because of the difference in therapeutic measures which are indicated.

I would like to ask the author if he considered making a more detailed histological distinction between glandular hypertrophy in the endometrium, and endometrial hyperplasia, the one meaning a simple enlargement or lengthening of the glands with a resulting thick endometrium which is liable to be found in patients with acyclic bleeding at any age, whereas, endometrial hyperplasia implies a piling up of surface epithelium of the gland itself and has a much greater pathological significance.

THE STATUS OF INTERNAL PODALIC VERSION IN OBSTETRICS*

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THE use of internal podalic version as a means of delivery has undergone a phase of transition during the past fifteen years, from a procedure which was performed frequently to one which today is done on relatively few occasions. This trend away from the use of version has been due to some extent to the adverse criticism of this procedure as well as to the more frequent use of cesarean section.

There are probably two reasons for the resort to cesarean section in cases in which a few years ago delivery would have been by version. First is the change brought about by the discovery and availability of penicillin. This has given the obstetrician more time to allow for a true test of labor, as it is very difficult in many cases to predict whether the head will go through the pelvis or whether the cervix will dilate satisfactorily, until the patient has been in labor twenty-four hours. Before the discovery of penicillin, one would certainly have to weigh the dangers of cesarean section in cases of prolonged labor against the dangers of version, and more often the decision would be in favor of the latter procedure. This decision was almost one of finality as there could be no turning back after version had been attempted, without doing a cesarean hysterectomy or taking the grave risk of peritonitis in performing a laparotrachelotomy. The growing popularity of the extraperitoneal cesarean section may to some extent have the opposite effect, in that one may still do this operation after failure to complete a version.

The second reason for the trend away from the use of version is the greater consciousness today of the midpelvic plane and of the outlet measurements due to the greater use and improvement of x-ray pelvimetry. Certainly one would not attempt a version in a case with borderline midpelvic or outlet x-ray measurements, especially in the android pelvis, although many of these types of patients were probably delivered successfully by version by obstetricians who today would not consider this procedure after viewing the x-ray plates. In this respect it is well recognized that a version is much easier to perform than a decomposition of a frank breech and extraction, as the head is molded and there is not the danger of intracranial damage as in bringing the unmolded aftercoming head through the pelvis in a breech presentation. The aftercoming head as a rule passes through the pelvis after version with less difficulty than in many cephalic deliveries. The feet are also more easily brought down in a version than in a frank breech.

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The method of version most generally accepted in principle today is that described by Irving W. Potter in his book published in 1922. Much of this book was devoted to answering criticism directed against him for his wide use of version and that criticism still stands today.

The anesthesia is the most important factor in the success of performing a skillful version. Potter used chloroform which certainly is the one of choice as far as obtaining relaxation of the uterus is concerned. However, because of the dangers associated with deep chloroform anesthesia and the suddenness with which the depth of anesthesia changes, ether is the anesthetic of choice today.

There is no place for spinal anesthesia in version as contractions of the uterus continue under this type of anesthesia. Nitrous oxide, cyclopropane, or combinations of these with ether do not give sufficient relaxation of the uterus. Deep anesthesia with ether by drop method gives the best relaxation of the uterus. Length of anesthesia is another important factor. It takes at least fifteen to twenty minutes to obtain surgical anesthesia with drop ether. If the anesthetic is begun fifteen minutes before ironing out the perineum and birth canal, by the time this is completed, there is usually sufficient relaxation of the uterus to complete the version.

One cannot overemphasize the necessity of complete relaxation of the uterus, as those who have done any appreciable number of versions have had the experience of having the uterus contract after inserting the arm. When this occurs the arm should be left in place until the depth of anesthesia is sufficient to relax the uterus. Any manipulation at this time is useless and may have dangerous consequences. One should not attempt a version in the presence of a contraction ring because of the danger of rupturing the uterus. When this complication is found to be present an extraperitoneal cesarean section should be performed. Another complication which may occur due to insufficient relaxation is "jackknifing" of the fetus, that is, when the feet are brought down through the inlet and before the head is pushed up out of the iliac fossa, the uterus contracts down thus preventing completion of the version.

The following is a brief summary of Potter's method of version:

1. The entire birth canal is ironed out gradually until the closed fist may be brought through the vagina. (Dr. Bill of Cleveland advocates doing an episiotomy in the nulliparous patient after the ironing out of the vagina and perineum before commencing the version.)

2. Potter advised the use of the left hand for version in all cases. (Bill advises the use of the left hand in left occiput positions and the right hand in right occiput positions as the palm of the hand then faces the feet which are more easily grasped in this position.)

3. The hand is passed through the cervix, avoiding the placenta, to the level of the feet. The feet are grasped and gentle traction is made, while the head is pushed up out of the iliac fossa by external pressure. Continued gentle traction is made until the knees are exposed, at which time the version is complete.

4. The anesthetic is now discontinued, and after a short rest, breech extraction may then be done.

In breech extraction Potter does not allow external pressure on the uterus until the shoulders are delivered as he believes that pressure on the head causes extension of the arms.

The generally accepted indications for podalic version when this method of delivery is used are: 1. shoulder presentation, 2, brow presentation, 3. face presentation, 4. occipitoposterior positions which do not descend to the mid-pelvis, 5. occipitotransverse positions which remain high, 6. prolapse of the cord when the cervix is dilated or dilatable, 7. second twin, 8. uterine inertia, and 9. placenta previa, which is often given as an indication for version, but the danger of producing an uncontrollable hemorrhage from the tearing of the lower uterine segment would almost eliminate this as an indication.

The following are rather interesting cases upon which internal podalic version and breech extraction were performed.

CASE 1.—A nulliparous patient, aged 22 years, was first seen in consultation after she had been in labor 80 hours. This patient was very nervous and had had a very poor type of labor. At this time the head was not engaged and was in left occiput posterior position. The cervix was dilated to 3 cm. in diameter. The uterine contractions were weak and irregular. The patient was given intravenous glucose and saline and sedation withheld. She was again seen in consultation twelve hours later after delivery by forceps had been attempted. Examination revealed the head to be at the level of the ischial spines and to the left occiputposterior. The dilatation of the cervix was complete. A modified Scanzoni rotation was performed but traction on the forceps revealed a definite resistance to the descent of the head. There was no apparent disproportion so a version and breech extraction were performed. The aftercoming head was delivered very easily. The baby, which weighed 9 pounds, 6 ounces, showed no ill effects from the delivery.

CASE 2.—A nulliparous patient, aged 26 years, had been in labor approximately 18 hours and had been fully dilated one and one-half hours. The presentation was brow and the position left frontoanterior. The presenting part was not engaged but was fixed in the inlet. Delivery was effected by internal podalic version.

CASE 3.—A para i whose previous delivery had been uncomplicated. Had had severe false labor pains for ten days, had been unable to obtain sufficient rest because of the pains, and appeared to be exhausted in spite of having been given sedatives. The patient was at term so she was admitted to hospital for induction of labor. A medical induction was commenced at 8:00 A.M. with castor oil and quinine. Eight hours later the head appeared to be engaging in the pelvis but labor had not become established. The membranes were stripped from the cervix and ruptured. No small parts were felt at this time. Labor was well established one and one-half hours later and three hours after the rupture of the membranes it was reported that small parts could be felt prolapsed below the head. The cervix was dilated to about 5 cm. in diameter. One and one-half hours later the cervix was fully dilated so the patient was prepared for delivery. The left foot and the right hand were found to be prolapsed, the head being in right occiputanterior position. An internal podalic version and breech extraction were performed with no difficulty. The baby's left lower leg and foot and the right arm were quite edematous, but otherwise he showed no ill effects. This case is of interest in that it is a rare presentation and also probably represents an error in judgment in that the membranes were ruptured before the head was definitely engaged.

CASE 4.—A 25-year-old primipara had had an apparently normal first delivery. She was seen first in consultation after delivery by version had been attempted, because of a prolapsed hand, without success. The patient had been in labor 5¼ hours and the diagnosis of shoulder presentation had not been made until the hand protruded from the vagina,

at which time the cervix was fully dilated. Examination revealed the right hand protruding from the vagina, the head in the right iliac fossa and the back anterior. The patient was given 0.5 c.c. of Adrenalin and deep ether anesthesia to relax the uterus. The arm and shoulder were pushed up out of the pelvis and an internal podalic version performed. The baby weighed 8 pounds, 10 ounces, and was normal.

CASE 5.—A multipara, aged 36 years, had had two previous deliveries both of which had been normal. The membranes had ruptured prior to admission to hospital and on admission the cervix was fully dilated. The patient was prepared for delivery. Vaginal examination revealed the head to be in right occiputotransverse position. On attempting manually to rotate the head anteriorly the cord prolapsed. Counter pressure was made on the head to relieve pressure on the cord until sufficient relaxation of the uterus could be obtained by ether anesthesia. Delivery was then completed by version and breech extraction. The baby was normal and showed no evidence of intracranial damage. Birth weight was 9 pounds, 5 ounces.

Summary

1. Internal podalic version and breech extraction are a very useful method of delivery with fairly definite indications for its use.

2. Ether is the anesthetic of choice for version.

3. Episiotomy done before commencing version in the nulliparous patient facilitates the delivery of the aftercoming head.

4. Delivery by internal podalic version entails less danger of intracranial injury than delivery of a breech presentation.

Discussion

DR. G. T. ALTIMAS.—Today a discussion of internal podalic version is timely because in obstetrical practice version has been almost discarded. Interns and residents get little encouragement in thinking about version and less in practicing it. Many obstetricians use version only on a second twin.

It could hardly be said that the author has defined the status of internal podalic version in present-day practice. The most that one could say is that some of the possibilities of version have been placed before us for consideration.

Proponents of delivery by internal podalic version have been inclined to make the operation appear simple. The speaker has done this in the four interesting cases which are presented. I take it that he would advocate delivery by version more frequently in cases of posterior position, incomplete descent of the head, and deep transverse arrest, as well as in the usual cases where version is indicated, such as transverse presentation, prolapsed cord, and other malpresentations.

When we read in the annual report of the Johns Hopkins Hospital for 1945 that midforceps were not applied once in over two thousand deliveries, we may wonder if some of the difficult forceps deliveries that version would avoid are really necessary. With penicillin, intravenous solutions, and the intelligent use of Pitocin, many of the difficulties are removed and difficult operations avoided.

Internal podalic version is a potentially dangerous procedure but the inherent damages can be avoided or overcome by following a carefully prepared plan in deciding when it should be done.

As in any art, it is practice that makes for perfection, and as version is practiced the results may be expected to improve with time, provided a careful set of contraindications is followed.

No mention has been made of displacement of the head where it has settled at least part way into the pelvis. This is a most important consideration because if the head is not easily displaced out of the pelvis one should be wary in attempting version.

The rupture of the membranes is not as serious a consideration as is often taught but the time of rupture is not to be considered unimportant. It is only in cases where the membranes have been ruptured for a considerable time that we find the uterus tightly molded about the body of the child and a contraction or retraction ring developing.

The cervix should be fully dilated or nearly so before any attempt at version is made, unless the life of the fetus is a secondary consideration in doing the version. Unfortunately, in following this reasoning many cases of uterine inertia never come into the group suitable for version because cesarean section is performed before the cervix is fully dilated.

The remarks on anesthesia are most important. Personally, I prefer chloroform but most highly trained anesthetists refuse to give chloroform for deep anesthesia and shun ether as being old-fashioned. Under the circumstances, it may be said that, as the assistance of trained anesthetists at delivery increases, the opportunity of performing internal podalic version successfully will tend to disappear. I say this because the most important factor in the success of internal podalic version is deep anesthesia—to the point of complete relaxation of the uterus. This point is not attained with any of the newer anesthetic agents.

THE VALUE OF VAGINAL CYTOLOGY IN OBSERVING THE PROGRESS UNDER RADIATION TREATMENT OF PATIENTS SUFFERING FROM CANCER OF THE CERVIX*

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DURING the past thirty years carcinoma of the cervix has been treated in the large majority of clinics with radiation. This method of therapy has been very satisfactory, but still results in an essential mortality of from 25 to 35 per cent, even in very early lesions. Recently, there has been a move to consider surgery as the best treatment in selected cases. The method by which these cases are selected is of great importance if the advantages of radiotherapeutic treatment are not to be denied in those cases for which it is adequate.

In 1947, a study was begun to follow with repeated vaginal smears all cases of carcinoma of the cervix under radiation treatment. It was proposed to attempt to predict during treatment the radiosensitivity of the tumors and, in any given case, the immediate efficacy of the treatment. The object was to find a method whereby the radioresistant tumors which are not identifiable until clinical spread demonstrates their presence could be recognized before such spread had occurred. Particular attention was centered on Stages I and II.

Material

Material for this study was drawn from the Gynaecological Clinic at the Ontario Institute for Radiotherapy, Toronto General Hospital. All patients coming under treatment regardless of their clinical classifications were followed. Smears were prepared according to the technique of Papanicolaou, using the suction aspirator on the pool in the posterior fornix of the vagina. Smears were collected on the initial visit to the Clinic, again before the initiation of treatment, whether high voltage or radium, and weekly during high-voltage therapy. If radium was applied before high voltage, a smear was made before the high voltage was begun. Smears were then collected at the regular follow-up examinations of the patients after the completion of treatment.

Out of 120 cases which were followed, fifty-four are presented in this report in which the regularity of the collection of smears justifies inclusion. In dealing with a large number of patients over a long period of time in a clinic, it was found difficult to insure the meticulous regularity of the collection of material necessary for any reliable reporting.

Radiation changes in both the normal vaginal cellular elements and in the malignant cells were observed. Where these changes were marked the smears usually cleared of malignant cells early in treatment and the response to radiation was judged to be good. In several, especially in Groups III and IV, little radiation effect was noted and the smears remained positive. Radiation changes in cell morphology add greatly to the difficulties of accurate interpretation of smears and contribute to the error of the observer.

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In this report, when the vaginal smear cleared of malignant cells before the twentieth high-voltage treatment and remained negative subsequently and the clinical course of the patient remained satisfactory, correlation between response to therapy and the clinical course of the patient is said to exist. In Stages I and II, this means no evidence of residual or recurrent disease. Correlation is also claimed when the smears remain positive and the clinical course of the patient is unsatisfactory. Lack of correlation is reported when the smears showed persistent viable carcinoma cells showing no radiation changes and the patient's clinical course was reported as satisfactory or when the smears were negative and the clinical course was downhill.

The group has been divided into those cases in which positive smears were obtained before the initiation of therapy, and those cases in which we were unable to make a diagnosis of carcinoma of the cervix by the same method.

TABLE I. CASES COMPLETELY FOLLOWED

Stages I and II		13
Stages III and IV		41
Total:		54
Pretreatment smears positive	40	
Pretreatment smears negative	14	
Stages I and II		13
Pretreatment smears positive	10	
Pretreatment smears negative	3	
Stages III and IV		41
Pretreatment smears positive	30	
Pretreatment smears negative	11	

The significance of the vaginal smear as a method of following the course of treatment is presented in the following tables. They show that when the pretreatment smears were positive, the correlation was absolute, but when the smears were negative, the reverse was true.

TABLE II. STAGES I AND II

Pretreatment smears positive	10
Correlation between vaginal smear findings and clinical course	10
Pretreatment smears negative	3
Correlation	0

TABLE III. STAGES III AND IV

Pretreatment smears positive	30
Correlation existed	20
Correlation percentage	66%
Pretreatment smears negative	11
Correlation existed	1
Correlation percentage	0.9%

All cases treated by radiation treatment in the Clinic are first diagnosed by biopsy.

The group of fourteen cases, three in Stages I and II and eleven in Stages III and IV, in which it was not possible to make a diagnosis by this method when biopsy was positive, are disappointing and puzzling. Several good smears from each patient were examined and reviewed and in none of these cases was there sufficient evidence to call them positive. The false negative reports from cases

in Stages III and IV were from patients with large ulcerating lesions and were probably due to the fact that a smear of the vaginal contents from such cases is made up of necrotic debris and blood, and the organized viable cells are at the periphery of such lesions rather than on the surface. This is of little consequence in this type of case from the diagnostic point of view since the nature of the lesion is so obvious.

The three cases in Stages I and II are more difficult to explain. Two of them were highly undifferentiated anaplastic carcinomas in young women. When first seen the lesions were large, but were reported as being confined to the cervix, and the cases were classified as Stage II. Both patients died of their disease eight and ten months after initial diagnosis. Their tumors must have been highly radioresistant and did not exfoliate. The third case should have been positive. It was Stage I tumor and the patient has done well and is apparently free of the disease.

Thirty-five cases which were followed for varying lengths of time are not included in the above series because the commencement of their treatment antedated the time when the investigation was started. They are mentioned because, on follow-up, twenty-seven were found to have clinical evidence of recurrent disease. Of these, fourteen showed no malignant cells on vaginal smears, while thirteen did. Several of these thirteen cases were submitted to biopsy as a result of a suspicious or positive report being obtained from examination of routine smears, when the clinical findings were satisfactory.

Returning to an analysis of the first group of patients, four patients, all Stage I cases, received 8,400 mg. hr. of radium, half intravaginal and half intrauterine. Four weeks after the application of radium and before their high-voltage treatment was started their smears were negative and have remained negative. Three of these patients are alive and well, fourteen to seventeen months later, and show no clinical evidence of disease. One patient whose case may be worth presenting in detail is interesting.

A diagnosis of Stage I cancer of the cervix was made in this 61-year-old patient in November, 1947. Smear at this time was positive. Between January 2 and 14, the patient received routine intravaginal and intrauterine radium. A smear prior to this therapy was again positive. High-voltage therapy began four weeks later and seven vaginal smears taken at regular intervals were negative. The patient was seen in Clinic at three-month intervals with negative smears until March, 1949, when her clinical report was satisfactory. A smear taken at this time, however, was interpreted as positive, as was a cervical scraping taken at the same time. This case should probably be regarded as persistent disease rather than recurrent carcinoma. The cervix healed following therapy and the smears cleared, but it is probable that islands of partially devitalized but not dead cells are sealed over by the proliferation of fibrous tissue and remain quiescent for varying lengths of time before proliferation begins again.

The other six patients in this group received high voltage initially and showed a clearing of malignant cells in smears after an average of 15 high-voltage treatments. This is calculated as 1,800 r to the cervix. All these patients were alive and well fourteen to twenty months later. Reference has already been made to the three patients we were unable to follow in this manner.

In the thirty cases of Stages III and IV diagnosed as malignant on vaginal smear, twenty cases showed correlation. In nine cases the smears showed high-voltage response and were read as negative after an average of eighteen high-voltage treatments. They have been judged as clinically improved on follow-up for from one to two years. Eleven cases showed positive smears throughout treatment and are all dead of their disease from two to twelve months after starting treatment or were moribund when last reported.

Ten cases showed no correlation. The patients fell into two equal groups. Five showed positive smears throughout treatment and have made satisfactory clinical progress up to the present, and in five cases the smears became negative and the patients have all died of their disease. In this group, the method was of no prognostic value. Eleven cases of Stages III and IV were not diagnosed as carcinoma on smear before treatment. Ten of them never gave a positive smear and all are dead of their disease. One case, referred to earlier, varied from this pattern. The patient had an initial negative smear, the first two during treatment were negative. Two positive smears were obtained, all subsequent ones were negative. The patient, a Stage III case, has shown clinical improvement for sixteen months.

If those patients who are not showing adequate response to radiation therapy and who are also suitable for surgery could be selected by some procedure before extensive radiation with its undesirable sequelae has been administered, it may be possible to increase the salvage rate in early cases where the lesion is confined to the cervix. This will be a small, but apparently a fixed percentage of cases. Salvage rates have improved remarkably with improved radiation methods, but an apparent plateau has been reached with this method of therapy.

This is a small series of cases, but there is some evidence from our findings that the use of this or an allied method of following these patients while under treatment is worth while. Repeated biopsy of the cervix has been tried and is technically impractical.

Summary

1. Thirteen cases of carcinoma of the cervix, Stages I and II, were followed with vaginal smears throughout the course of their radiological treatment. In all cases where the initial smears were positive, correlation existed with the clinical course of the disease.

2. Forty-one cases of carcinoma of the cervix, Stages III and IV, were similarly followed. In those cases in which a positive initial diagnosis of carcinoma was made by this method, correlation existed in 66 per cent of cases.

3. Based on this small number of patients, some evidence exists that vaginal smears have value in assessing the radiosensitivity of a tumor of the cervix. If this is so, tumors which show evidence of radioresistance at an early stage in radiological treatment could be selected and treated surgically.

Discussion

DR. ETHLYN TRAPP, Vancouver, B. C.—The establishment of the author's thesis would make possible the salvaging, by means of radical surgery, those Stage I cases of cancer of the cervix which radiation does not cure. Until quite recently, with the recognition of intraepithelial cancer as a cancerous rather than a precancerous lesion, these have been about 25 per cent of all Stage I cases.

It is generally recognized that the failure to cure Stage I cancer of the cervix by radiation treatment is due to one of three reasons:

1. Disease has already spread beyond the cervix, usually to the pelvic lymph nodes.
2. Radiation treatment has been inadequate.
3. The cancer is radioresistant.

With respect to the first, we are all familiar with Taussig's work on the dissection of the pelvic lymph nodes in an effort to increase the salvage rate in this group of cases. A combination of radiation and iliac lymphadenectomy could be a partial answer to the problem and such a procedure is being carried out in several places.

Too many reports have been published comparing the results of the best possible surgery with those of less than the best radiation therapy, or, in other words, really adequate surgery with less than adequate radiation therapy. Radiation therapists feel that this situation has prevented Ruth Graham's distinguished work from being as valuable a contribution to the problem as it might otherwise have been.

The cancer is radioresistant, that is, it is incurable by radiation because of the nature of its cells; the proving or disproving of this is of great importance to both surgeons and radiologists. The recent use of exfoliated cells for this purpose follows long years of research on this subject, namely, the attempt to estimate the radiosensitivity of cancer cells.

Early in the history of radiation therapy the belief became prevalent that the cells of anaplastic tumors were more sensitive to radiation and therefore more curable than were the more differentiated types of cancer cells. Sir Stanford Cade of London in *Malignant Disease and Its Treatment by Radium*, says of these so-called radiosensitive tumors "... they are the 'miracles' of radiation, the source of conceit in the inexperienced radiotherapist, and the greatest source of disappointment when apparently brilliant successes become in due course dismal failures." This belief has been difficult to eradicate in spite of the fact that work in many research centers has proved the contrary to be true.

In 1930 Glucksmann and Spear at the Strangeway Laboratories in Cambridge began to take serial biopsies in cases before and during treatment in order to determine the relationship between radiosensitivity and radiocurability. This work has extended over the intervening years and it has been shown consistently that the radiosensitivity of tumor tissue is not linked with its radiocurability but that the preponderance of undifferentiated cells, that is, its anaplasia, determines the degree of radiosensitivity, while on the other hand the radiocurability varies with the degree of the differentiation and inversely with the rate of growth. They have also shown that the capacity for increased differentiation under radiation distinguishes most of the radiocurable tumors.

Lacassagne in Paris was one of the very early workers in this field. He experimented with many types of biological material and demonstrated repeatedly that 2 to 3 per cent of all such material is radioresistant. For example, if a group of laboratory animals is exposed to a lethal dose of x-ray, 97 to 98 per cent will be dead, while the remaining 2 to 3 per cent survive for reasons we do not know. The recent experiments at Bikini proved the same thing.

On the basis of all this work it seems reasonable to suppose that an equally small percentage of cancer of the cervix is radioresistant. This brings me to the point that apart from this small percentage, radiation therapists believe that all Stage I cancers of the cervix are curable by radiation and that if cure is not obtained it is because of one of the reasons previously mentioned.

The work reported by Ruth Graham is based on a very low dosage of radiation. Dr. Wildermuth at the Tumor Institute of the Swedish Hospital in Seattle, has been working on the same problem but using practically twice her dosage of both radium and x-ray. He uses a schedule of x-ray dosage of 3,200 r to each of four pelvic ports in six weeks, avoiding the central 4 cm. band. After twenty days of treatment, he found that exfoliated cells still showed malignancy while following radium treatment of 8,000 mg. hr., irrespective of whether it was given before or after x-ray, radiation effects were seen in a week and in every case so treated there were negative vaginal smears.

It is to be hoped that Dr. Maloney and her associates continue with this project. The present percentage of error is too great to draw conclusions and Dr. Maloney makes no attempt to do this. Questions come to mind. One wonders why any biopsy-proved cases should have negative smears; there were quite a number of these, 14 out of 54. Do some cancers not exfoliate their cells or would more slides and further search have found them? More investigation should bring the answer to this and other questions.

Dr. Maloney is in an ideal position to carry on this work with a large clinic, experienced gynecologists, pathologists, and radiation therapists, and last, but not least,

a physicist, for it is essential for any valid conclusion to have the exact amount of tumor dosage correlated with the radiation effect. It is on this point that all the published work that I have seen falls short. Radiation dosage is too often reported in terms of roentgens given off by x-ray or radium sources rather than those received by the tissue under treatment.

My own opinion is that the radiocurability of cancer of the cervix depends predominately on other factors than the type of tumor cells and their immediate response to radiation. Research such as is being done at the Ontario Institute of Radiotherapy and other centers must eventually bring us the truth. Perhaps in the meantime other research may discover more certain means of curing cancer of the cervix than either surgery or radiation.

DR. W. A. SCOTT, Toronto. Ont.—It is rather interesting that a suggestion regarding the value of this type of investigation was made almost three years ago by Warren Shields in his handbook, *Vaginal Cytology.* He states, "From the point of view of actual numbers of patients who may be benefited by the use of the vaginal smear, those who have been irradiated for cancer will probably form the largest group. Although there have been no reports of systematic follow-up with the vaginal smear of cases treated for cancer by irradiation, it is our impression that the effectiveness of treatment as to both initial response and recurrence may be more easily gauged by the vaginal smear than by any other means." During the last five or six years, a problem that was thought to be moribund, if not dead, had been revived; namely, the relation of surgery versus radiotherapy in the treatment of cancer of the cervix. The principal argument for surgery is the undoubted fact that a certain number of these cancers are radioresistant, and if these cases could be picked out early the line of treatment for any particular case would be distinctly marked out. Unfortunately this cannot be done. Therefore, the proponents of radical surgery in the treatment of cervical carcinoma tend to treat all early cases surgically. I recognize that the investigation carried out by Dr. Maloney does not solve this problem, but it does appear to be of real worth in evaluating radiological treatment during its progress. If further investigation of larger series by Dr. Maloney and her associates, as well as by other investigators, should prove that what appears to be the obvious conclusions of this morning are validated, we might have a method of picking out certain cases in which change from radiological to surgical treatment might be advisable early in the progress of such treatment. That, in itself, would be an advantage because I believe that the pendulum is going to sway too far toward the surgical treatment of cervical carcinoma.

Original Communications

TIME OF OVULATION*

A Correlation Between Basal Temperature, the Appearance of the Endometrium, and the Appearance of the Ovary

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DETERMINATION of ovulation time in women has been a subject of great interest to investigators for many years. Its obvious importance in the field of human fertility is such that many techniques have been devised whereby the ovulation date could be identified. Changes in the mucosa of the genital tract, in electrical potential, in temperature, and in the hormonal constituents of the body are but a few of the diagnostic procedures attempted in recent years. It is unnecessary here to review the voluminous literature which many years ago assumed that ovulation occurred at about the time of menstruation and which has since by the use of various modern investigative techniques determined its occurrence to be at about the middle of the normal menstrual cycle.

The main difficulty in identifying ovulation time has been, of course, the impossibility of directly observing the ovary from time to time during the cycle. It has been necessary to search for and identify other simultaneous measurable physiological phenomena which had some relationship to ovulation and the presence of which would therefore permit the supposition that ovulation had occurred. Disregarding the subjective symptoms which are said to occur occasionally at the time of ovulation, the indirect physiological activities most frequently used at the present time to interpret follicle rupture and corpus luteum formation are as follows:

1. Changes in urinary excretion of hormonal products.
2. Changes in the epithelium of the genital tract.
3. Changes in basal body temperature.

In the past all these phenomena have been checked one against the other. Some of them have also been checked against the measurement of the age of recovered ova or of the appearance and segmentation of fertilized ova. A few attempts have been made to check one or more of these factors against the actual appearance of the ovary itself with its apparent proof of ovulation in the form of a fresh corpus luteum. In the latter case, however, it has been found that the gross appearance of the fresh corpus luteum may give a deceptive im-

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pression as to its actual age, and it was found necessary to examine the structure microscopically in order to determine the number of hours and days of its development. Even then there is some disagreement concerning the microscopic characteristics which a corpus luteum presents at the age of 12 hours, 1, 2, or 3 days. After all, it is an extremely difficult problem to determine the exact moment at which the ruptured follicle extrudes the ovum and begins its development as a corpus luteum.

That ovulation occurs around the middle of a normal 28-day menstrual cycle is now a fairly well-established fact, but the time of ovulation may vary a great deal and even the once prevalent theory that ovulation precedes menstruation by a fairly standard 14 days has now been disproved both in monkeys and human beings (Hartman,[1] Buxton[2]).

The first recent attempts to ascertain indirectly the ovulation date by observation of correlated phenomena consisted largely of noticing the coincidence of two or more of these bodily changes, with what was generally considered to be approximately the date of ovulation. In 1940 Rubenstein[3] noted that the basal body temperature, which dropped and then rose at about midcycle, made its definite upward shift at the same time as a change, possibly representing ovulation, occurred in the vaginal smear.

In 1943, D'Amour[4] followed twenty cycles in five subjects, using as indirect evidence of ovulation six criteria: (1) subjective experience (ovulation pain), (2) basal body temperature charts, (3) estrogen assays, (4) gonadotrophin assays, (5) pregnandiol determination, and (6) vaginal smear.

He found a peak of estrogen shortly followed by a gonadotrophin peak at midcycle which was in turn followed by an excretion of pregnandiol and a change in the vaginal smear. He concluded that the gonadotrophin peak was probably the most accurate indication of ovulation although there was no actual observation of the ovary in these cases.

Using a number of patients requiring elective operations, Greulich[5] correlated temperature charts with actual observation of the ovary at the time of ovulation. Although there was a general coincidence of temperature rise with the appearance of new corpora lutea (as observed microscopically), the discrepancy in time relationship was still such that there was an apparent variation of 2 or 3 days at least in the time of ovulation as indicated by the temperature rise and the actual microscopic appearance in the ovary. Brewer and Jones[6] found by actual observation at laparotomy that ovulation generally occurred at about midcycle but, since the elective operations observed involved hysterectomy or other pelvic procedure, they naturally could not determine how near to the next menstruation the ovulation occurred.

A correlation between temperature charts and endometrial biopsy findings was made by Martin[7] in 1943 not necessarily to identify the actual time of ovulation but to find if the postovulatory temperature rise corresponded with secretory changes in the endometrium. He observed that forty-seven patients with "biphasic" temperature charts produced normal premenstrual secretory endometrium whereas nine patients with "monophasic" or anovulatory charts had proliferative endometrium with no evidence of secretory change.

These various techniques for the determination of ovulation time are naturally of great scientific interest. For the purpose of clinical application, however, most of them have obvious disadvantages.

Urinary assays of gonadotrophin, even granting their accuracy, are difficult, inconvenient, and time consuming, and, by the time the assay is finished, ovulation has long since passed. The endometrial biopsy and pregnandiol determination also identify ovulation only when it is past and are therefore practical only in determining whether or not a patient has ovulated previously. The vaginal-smear technique is admittedly difficult (Papanicolaou,[8]) and, although it can be read quickly, its interpretation takes extensive training and practice.

Therefore, the basal body temperature technique remains as the only practical means whereby a patient or doctor can determine, at a clinically useful time, the date of ovulation. The question is whether or not this temperature change is a sufficiently accurate chronological index of ovulation to make it really clinically useful.

Except for Greulich's[5] series on inmates of a mental institution, there are no data which prove, by actual ovarian observation, that the characteristic midcycle temperature rise is coincidental with the phenomenon of ovulation, nor has this phenomenon been accurately correlated with changes in endometrial biopsy.

It was, therefore, decided to observe the ovary and the endometrium at the time of ovulation, as identified by basal body temperature change, in patients who were to have elective operations for fibromyomas of the uterus or other pelvic pathology, and to compare, and attempt to correlate, the microscopic appearance of the corpus luteum and endometrium with the midcycle changes in temperature.

The identification of the age of the corpus luteum from its microscopic appearance has been studied both in the monkey and the human being.[5, 9, 10] Corner's data concerning the early changes in the monkey bear a striking similarity, as might be expected, to the changes following ovulation in the human ovary, and it is possible to establish the age of the corpus luteum in the monkey to within about twenty-four hours.

The endometrium also undergoes fully as definite changes during the time of ovulation and it was thought that a further check with endometrial material would aid in the temperature-change correlation.

Material

To carry out this observation, twenty-three patients on the waiting list for gynecological operations at the Sloane Hospital for Women were taught how to make temperature records, and were followed for a month or more to find if their charts showed any regularity. Patients for the most part had a diagnosis of fibromyomas of the uterus, although there were others with endometriosis or waiting for tubal plastic operations. Eighteen of the twenty-three patients proved acceptable for study. Since their case histories and findings at operation, except for the endometrium and corpus luteum, are not particularly relevant, they will not be discussed.

Patients were admitted to the hospital several days before the expected temperature rise so that their temperature charts would be well stabilized in their new environment. All patients were operated upon on the day on which their temperatures showed the characteristic rise indicative of ovulation. This rise, of course, may actually represent a variation of about 24 hours in determining ovulation time, because it is conceivable that ovulation may possibly

have occurred shortly after the previous day's temperature was taken and not been identified until the subsequent rise 24 hours later was seen. On the other hand, ovulation may have occurred only a few hours before the temperature was taken which indicated the ovulatory rise. It would be difficult if not impossible to eliminate this time variable. Since only *basal* body temperatures are indicative of the change produced by ovulation it would theoretically be necessary to keep a patient at complete basal rest and to take hourly temperature readings to narrow down the ovulatory temperature change more accurately.

Furthermore, when the temperature rise was noticed in the morning there was a variation in time between the observation of the temperature rise and the hour in which the patient could be placed on the operative schedule. Occasionally the operation did not take place until around noon. Therefore, with the previously mentioned possibility of delay in identification of ovulation, and the subsequent delay in operation there may reasonably have been a variation of almost 30 hours between the time of ovulation and the time of operation in these patients, even though they were all done on the morning when the change in temperature was first noticed.

Observations

At the time of operation an endometrial biopsy was obtained if the uterus was not removed and both ovaries were carefully examined. If what appeared to be a corpus luteum was present, this was excised for microscopic examination. The histological appearances of the endometrium and of the excised corpus luteum were then compared with the basal body temperature chart and an attempt made to correlate this data.

The interpretation of the age of the corpus luteum in days, to say nothing of the interpretation in terms of hours, is difficult because there is some disagreement among authorities as to what the exact measurable criteria are for the determination of luteal age. For the purposes of this discussion it might be advantageous to review a few of these criteria.

Immediately following the extrusion of the ovum from the follicle, the cells lining the follicle still appear granulosal in type. Within 12 hours, however, their mitoses disappear and they increase in size, and, partially losing their cellular membrane, they develop a syncytial appearance and accumulate fat droplets. As this development goes on, fibroblasts appear at the theca interna level and the theca interna itself is thrown into triangular cones with engorged capillaries.

At about 24 hours there is an ingrowth of fibroblastic cells into the former granulosal layer and the granulosal, or early lutein cells, as they should now be called, tend to arrange themselves radially.

Invasion of the new lutein layer by capillaries is thought not to begin until about 36 hours post ovulation when, as Corner expresses it, capillaries are "freely spouting into the granulosa," especially at the tips of the thecal folds. By this time connective-tissue cells have begun to encapsulate the hemorrhagic contents of the central cavity, and the lutein cells have developed a definite radial arrangement.

Vascularization by the end of 48 hours becomes one of the most characteristic attributes. In the corpus luteum of this age and by the time it is 72 hours old, vessels have reached the inner surface of the lutein layer and have even extended into the fibrin net of the central cavity.

By this time also the basal portion of cells in the lutein layer have filled out, there are no more fluid spaces, and the theca cells can't be well identified. Here again, the vascularity of the lutein layer is most characteristic.

Attempts have been made to classify the eighteen patients in this study into chronological groups as measured by the age of their corpora lutea. It

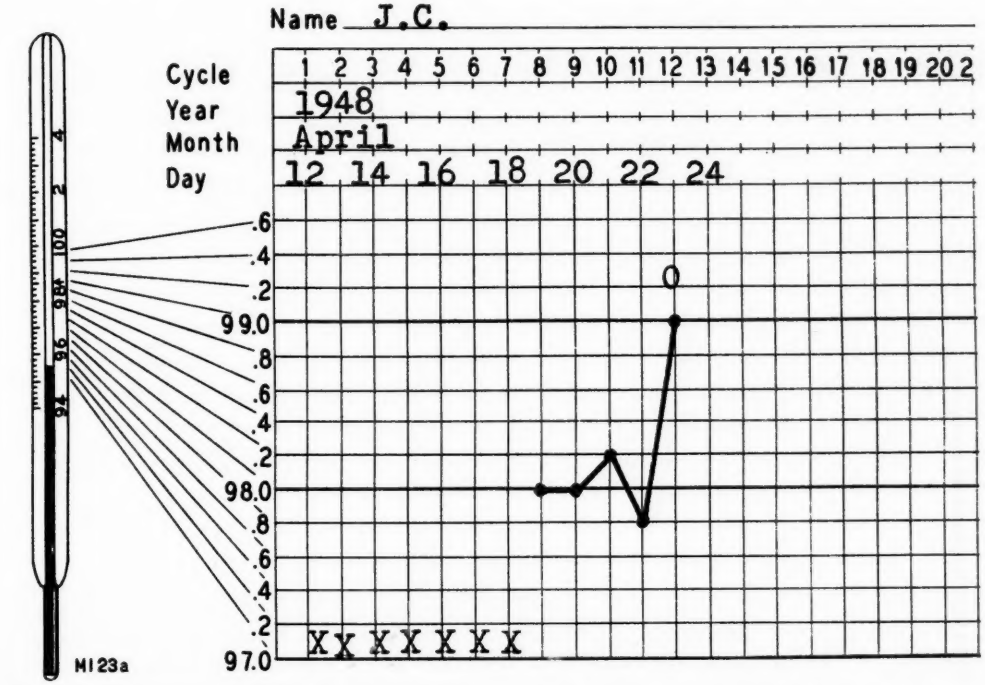
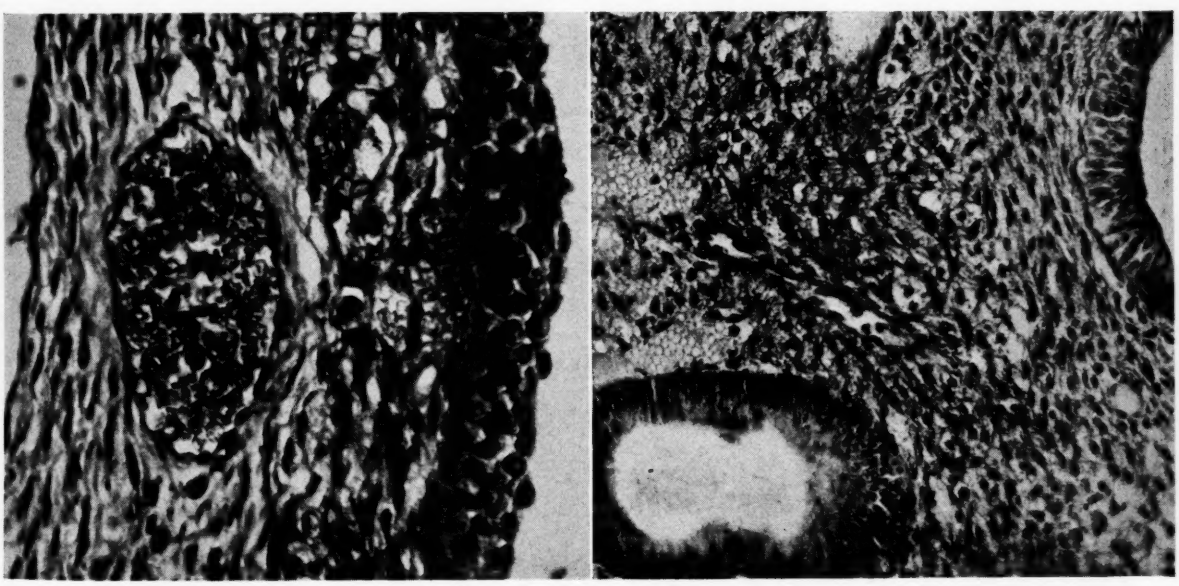


Fig. 1*A*.—Temperature chart of patient J. C. operated upon for fibromyomas of the uterus at time of temperature rise. 0 = date of operation.



B. *C.*

Fig. 1*B*.—Photomicrograph of the granulosal and subgranulosal layer of the furthest developed follicle in ovary of patient whose temperature chart is demonstrated in Fig. 1*A*. Note the absence of a well-developed theca-interna layer or other indication of imminent ovulation. (×567.)

Fig. 1*C*.—Endometrium at time of operation on patient J. C. Mitotic figures, stratified nuclei, absence of basal vacuoles denote estrogen activity with no indication of progestational activity. (×301.)

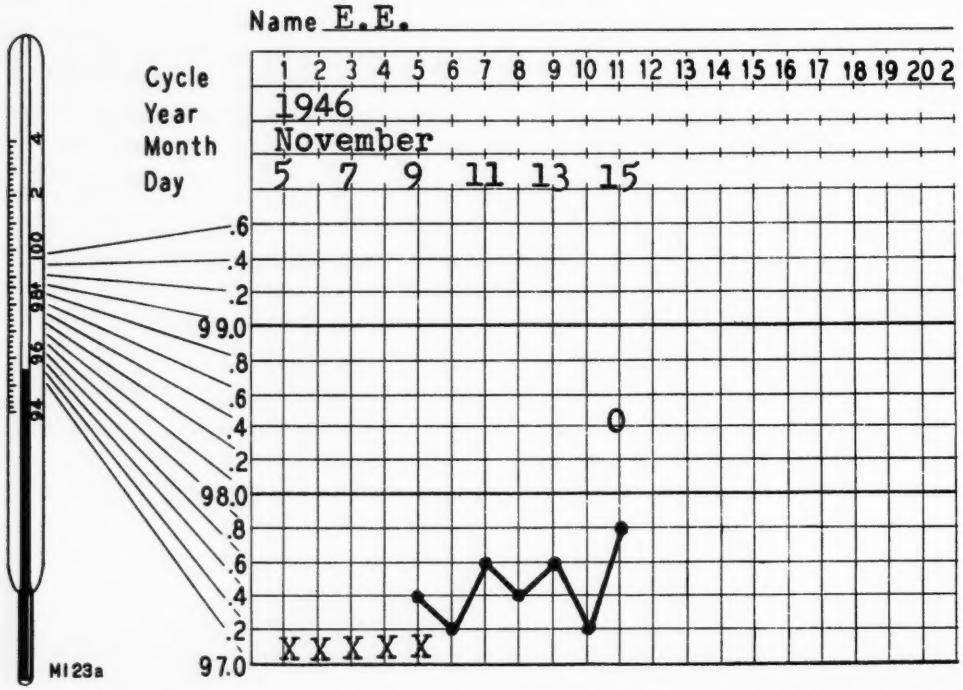
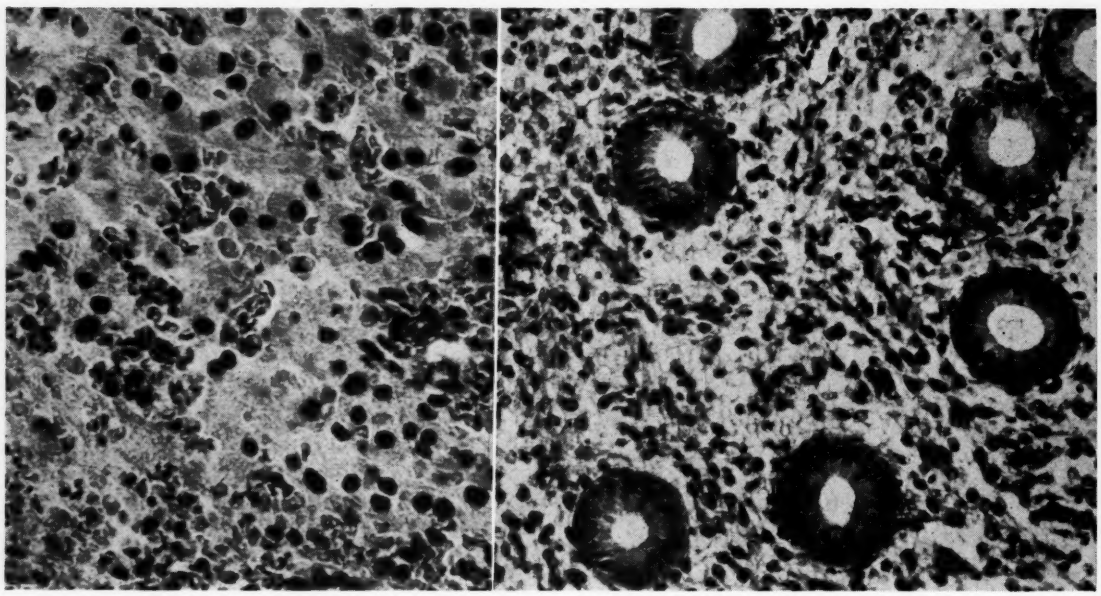


Fig. 2*A*.—Temperature chart of patient E. E. operated upon for suspected endometriosis at time of midcycle temperature rise. 0 = date of operation.



B. *C.*

Fig. 2*B*.—Photomicrograph of early corpus luteum removed from ovary of patient E. E. at laparotomy done at time of midcycle temperature rise. Note the loose, dissociated, and irregular early lutein cells and scattered areas of hemorrhage. The syncytial appearance of the cells and the absence of any cordlike radial symmetry denote a very early corpus luteum. (×567.)

Fig. 2*C*.—Endometrium removed by biopsy at time of operation on patient E. E. Small regular glands with basal nuclei and occasional mitoses show absence of any progestational activity. (×300.)

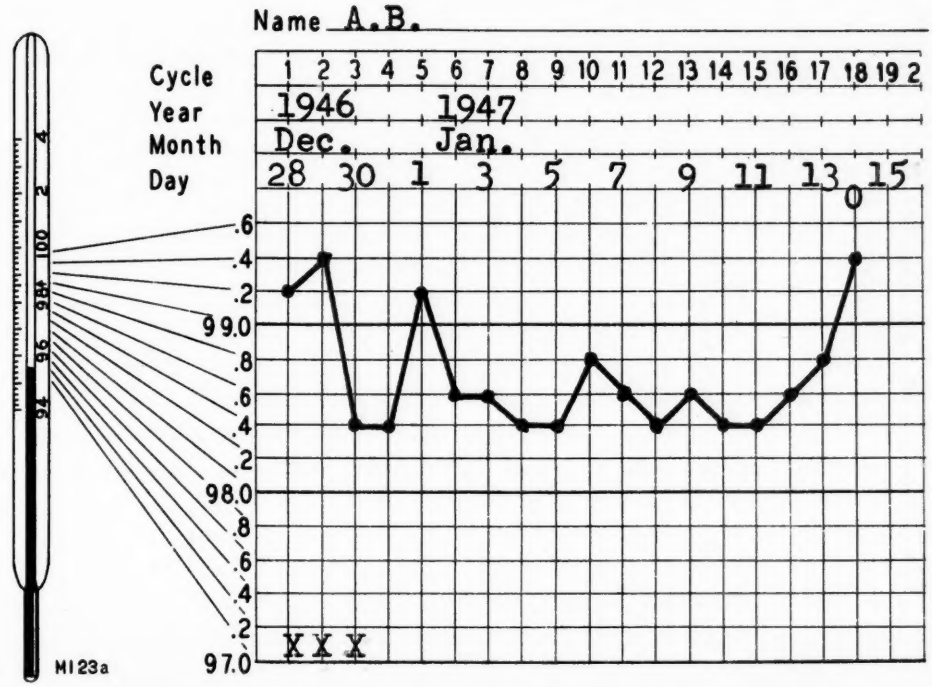
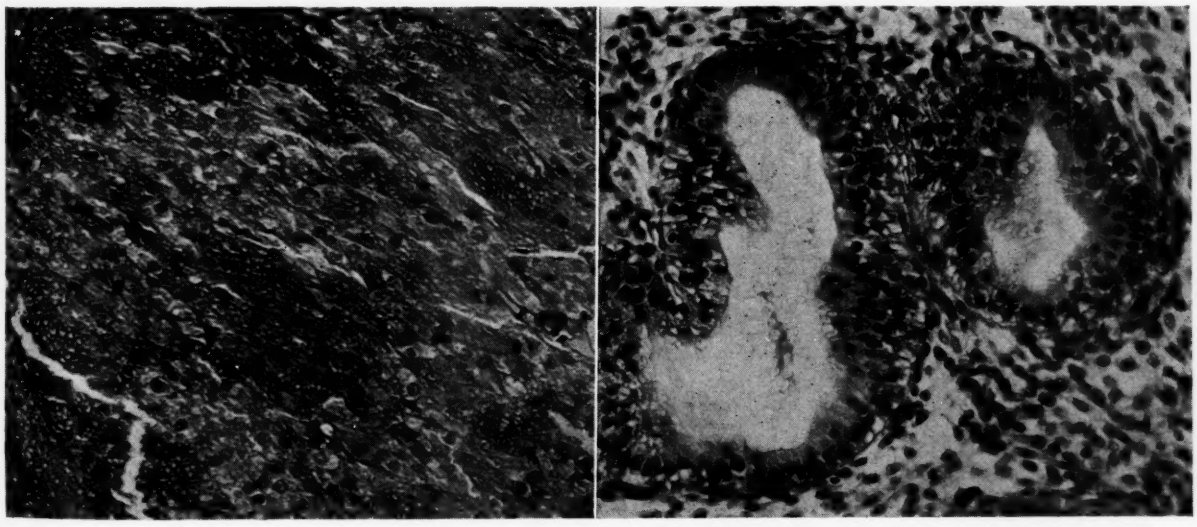


Fig. 3*A*.—Temperature chart of patient A. B. operated upon for fibromyomas of the uterus at time of midcycle temperature rise. 0 = date of operation.



B. *C.*

Fig. 3*B*.—Photomicrograph of corpus luteum removed from ovary of patient A. B. at laparotomy at time of midcycle temperature rise. The lutein cells have developed a radial arrangement and the lutein layer has developed a scalloped appearance as a result of constriction by the follicular cavity. Capillaries are rapidly developing throughout the cellular layer. The picture represents a corpus luteum with a probable age of about 36 hours. (×250.)

Fig. 3*C*.—Endometrium at time of operation on patient A. B. which shows estrogenic activity in form of mitoses and stratified nuclei in glandular epithelial cells. The presence of basal nuclei, however, represents beginning progestational response. (×300.)

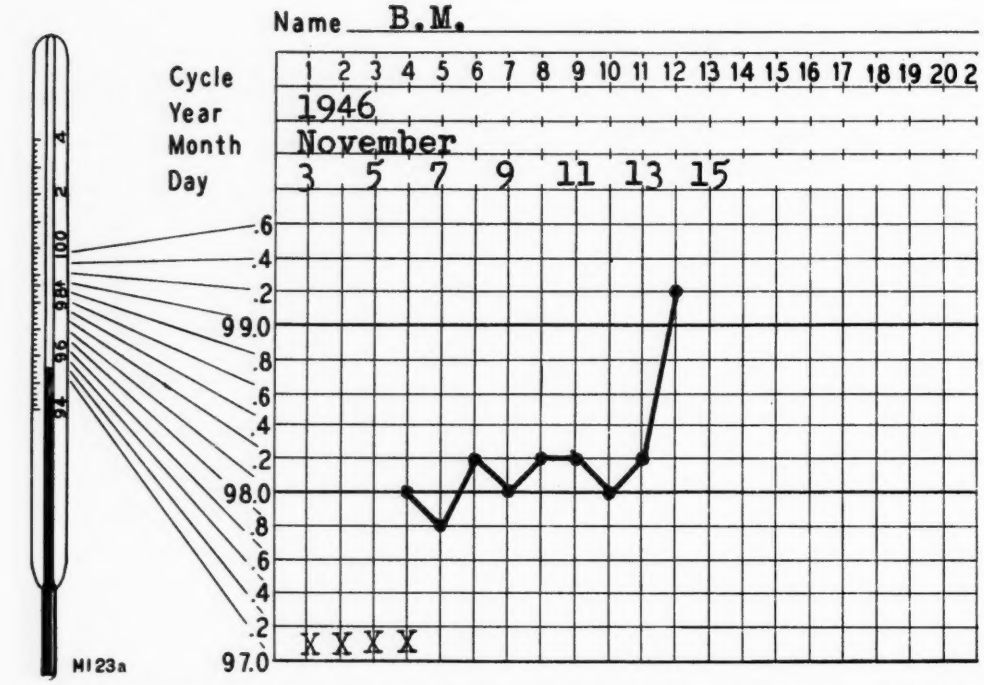
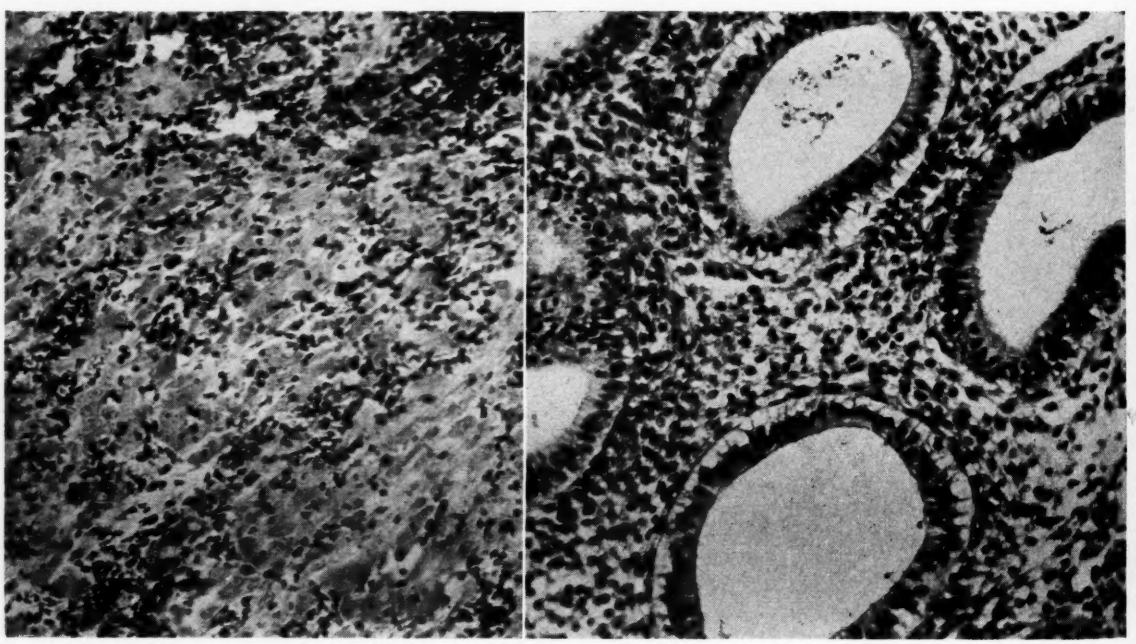


Fig. 4*A*.—Temperature chart of patient B. M. operated upon for fibromyomas of the uterus at time of midcycle temperature rise.



B. *C.*

Fig. 4*B*.—Photomicrograph of corpus luteum of patient B. M. who was operated upon at time of midcycle temperature rise. The lutein cells are well arranged in radial formation, the theca layer (not represented in the photograph) has developed a tufted appearance, and capillaries have extended throughout the lutein layer as far as the central hemorrhagic zone. (×250.)

Fig. 4*C*.—Endometrium removed from patient B. M. at the time of laparotomy. The glandular epithelial cells have begun the developement of basal vacuoles indicating progestational activity. No mitoses are observed. (×300.)

must be remembered that all of these patients had their operations at the time of their midcycle temperature rise. Six have fallen into the group in which we have no definite evidence of ovulation having occurred as yet. Two have fallen into the group in which the corpora lutea are very fresh, possibly under 12 hours of age; four have corpora lutea which we judge to be about 24 hours old; two each with a corpus luteum of about 36 hours; and two each of 48 hours and 72 hours of age or possibly longer (Table I). Certainly these conclusions as to age are relative and, although we would not be so sanguine as to try to state exactly their definite age, we are confident in stating that they are in different stages of maturity.

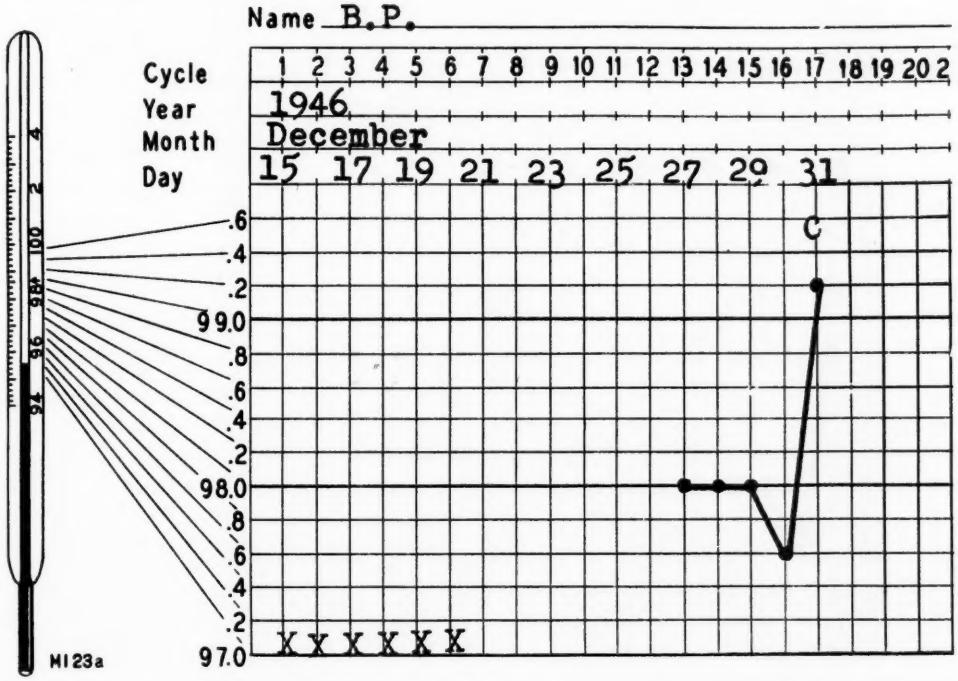


Fig. 54.—Basal temperature chart of patient B. P. operated upon for fibromyomas of the uterus at the time of midcycle temperature rise. 0 = date of operation.

The endometriums, on the other hand, show much less progressive change actually than do the corpora lutea. There seems to be a delay in the appearance of secretory change, so that evidence of luteal activity in the endometrial tissue does not appear, in this series at least, until the corpora lutea are at least 36 hours old.

TABLE I. DISTRIBUTION OF EIGHTEEN PATIENTS OPERATED UPON AT TIME OF BASAL BODY TEMPERATURE RISE. DISTRIBUTION IS IN TERMS OF ESTIMATES OF THE AGES OF CORPORA LUTEA REMOVED AND EXAMINED MICROSCOPICALLY

	OVULATION (AS DETERMINED BY BASAL BODY TEMPERATURE RISE) ↓					
LUTEAL AGE (AS DETERMINED MICROSCOPICALLY)	PRE-OVULATORY	12 HOURS	24 HOURS	36 HOURS	48 HOURS	72 HOURS
No. of patients in each luteal age group	6	2	4	2	2	2

B.

C.

Fig. 5*B*.—Photomicrograph of the corpus luteum removed at laparotomy done at time of midcycle temperature rise on patient B. P. The theca-interna layer, one edge of which is seen at the lower left, is thrown into characteristic tufts, the lutein cells have developed a radial arrangement interspersed with capillaries which extend as far as the central lumen and frequent vacuoles appear in the lutein cells. (×567.)

Fig. 5*C*.—Endometrium removed at same time as above corpus luteum on patient B. P. Note the greatly increased vacuolization along the epithelial basement membrane, representing progestational activity. (×300.)

It will, therefore, be seen that although all these patients were operated on on the morning of their temperature rises, they exhibited considerable difference in the histological pictures of their corpora lutea and endometriums. In spite of the before-mentioned possible variation of 24 to 36 hours which might be a normal technical variant, there is still a certain amount of variation in the luteal age which indicates that the ovulatory temperature rise is not entirely simultaneous with the time of ovulation. Figs. 1*A* through 5*C* graphically represent this difference in luteal age.

Comment

Inspection of the various temperature charts discloses the fact that patients were operated upon at the time of the midcycle temperature rise. This midcycle rise varies considerably in different cases, as might be expected, but for the most part the rise is a sudden definite one. Although the patients were operated upon at the time of the temperature rise, the microscopic inspection of the various corpora lutea and endometriums disclosed a variation in luteal age of at least 3 and possibly 4 days. It has been demonstrated elsewhere that the cause of the ovulatory temperature rise and its postovulatory maintenance probably is the presence of progesterone in the ovulating individual.[11, 12] Therefore, it seems reasonable to assume that there may be some variation in the time at which different corpora lutea begin to elaborate progesterone. It may even be true that, as occurs in some animals, progesterone is secreted by the theca-interna cells of the follicle even before ovulation occurs.

Furthermore, it is somewhat inconsistent that evidence of progestational activity is observed in the temperature charts but, in several instances, not until several days later in the endometriums. Can we assume, on this evidence, that a higher progestational titer is necessary to affect the endometrium than it takes to raise the basal body temperature?

How, then, is one going to instruct patients concerning the optimal time for conception in terms of the use of temperature charts as ovulation indicators. Patients frequently ask the exact time of ovulation in relation to the midcycle rise—whether it occurs the day before, at the bottom or top of the rise, or after the rise is accomplished. It is apparent that, even if the rise is abrupt, this question cannot be answered, and we have not even considered those many confusing cases so frequently seen of gradual rise at midcycle, requiring possibly three or four days.

Very possibly, then, the rigid use of temperature charts as ovulation indicators is a mistake. Evidence presented here certainly indicates considerable inconsistency in time relationships between temperature rise and luteal age—as much as 4 days' variation. Therefore, it seems legitimate to conclude that patients who use temperature charts must be told that they are only approximate indicators of ovulation time.

Summary

1. Various indirect methods of identifying ovulation time are discussed. They are basically (a) changes in urinary secretion of hormonal products, (b) changes in the epithelium of the genital tract, and (c) changes in basal body temperature.

2. The technique most easily available for the identification of ovulation time is the basal body temperature.

3. The purpose of this paper is to investigate the accuracy of the basal body temperature as an indicator of ovulation.

4. The basal body temperature charts in 18 cases are compared with the findings in the endometrium and in the ovary at laparotomy.

5. From microscopic observation of excised corpora lutea and of endometriums it is determined that the midcycle rise in basal body temperature may produce an error of as much as four days in determining ovulation time.

6. It is, therefore, not considered a sufficiently accurate indicator of ovulation time to permit its use clinically unless there is a clear understanding of its limitations.

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Discussion

DR. ENGLE (by invitation).—We have known for a long while that the basal temperature chart was an approximation. I think that the paper has given us a measure of the degree of variability of the body temperature which we did not appreciate before and which we regarded with a good deal of skepticism. In noting these cases I have been very much impressed with the few showing a temperature rise with perfectly normal follicles and no evidence of luteinization.

In studies that Dr. Buxton has done, there was valid evidence that the life span of the corpus luteum was 12 days, but in certain selected cases it could be as short as 6 or 8 days. If the corpus luteum takes a longer time than 48 hours to begin to elaborate its hormone, progesterone, that is another measure of variability.

I am not convinced that the theca interna creates much progesterone before ovulation. I do not see it in the removed ovary or the excised portion of a follicle in the theca. It might be true. Some animal experiments indicate that it is true. I am still resistant to that concept in the human being. In some individuals it may take a longer time for the corpus luteum to be formed and for its newly formed cells to begin to elaborate their specific lipid products connected with this particular hormone. I will depend much more on the histology of the uterine mucosa, as an indication of estrogenic or progestational action and as an indication of ovulation than anything else.

DR. HOWARD C. TAYLOR, JR.—The important point to decide is just exactly what practical significance Dr. Buxton's observations have; or, to put it the other way, how much his observations undermine our confidence in the rise of the body temperature in determining ovulation time. He has shown pretty well in the corpora lutea that he has obtained that there is a lack of correlation between the time of formation of the corpora lutea and the rise in temperature. I think he has offered two alternative explanations for this lack of apparent correlation—one, the possibility of a lack of physiological correlation, that actually the temperature rise does not correspond with the earliest hours

of the formation of the corpus luteum and, perhaps, the beginning of progestin formation; two, he may have demonstrated that we have made a mistake in estimation of the correlation between the two physiological phenomena. I believe he has left open the possibility that this lack of correlation is an artefact. He has said that no patient can be kept starving completely at rest.

DR. RICHARD N. PIERSON.—From what has been said it is difficult to know what to tell patients as to the time of ovulation. It seems to me we can conclude only that the determination of the ovulation time by the basal body temperature is at best unsatisfactory and difficult.

I would like to ask Dr. Buxton from his experience at the Sloane Hospital whether he still thinks in his clinic practice that there is an advantage in carrying on these tests. I think it is clear to us, from the emotional point of view of our patients, that there are some advantages in having patients do a thing like this if they know it is good.

DR. GERARD L. MOENCH.—I believe it is perhaps easier to explain the rise of temperature as being due to the associated hemorrhage present in the corpus luteum, but the question is: Why the drop in temperature? The patients I see certainly do not run typical temperatures; in fact, they are more irregular than regular, and those of us who do artificial inseminations today generally pick out the supposedly fertile week calculated from the days of menstruation for the last six or twelve months and do inseminations at forty-eight hour intervals during that time, without any regard to the basal temperature charts.

DR. BUXTON (Closing).—In answer to Dr. Gepfert, I would say that these patients were between 25 and 40 years of age and had histories of normal cycles.

As far as Dr. Hughes' comment goes, there apparently is frequently a fall before the temperature rise. It is always shown on the chart which has been manufactured, but why there is a fall I think nobody knows. I believe one of the few things that these cases show is that the temperature rise occurs at different times as far as ovulation is concerned.

Dr. Taylor desired to know whether the basal body temperature really should be depended upon clinically and the cause of the apparent discrepancy between the changes in the corpus luteum and the time that the temperature rise actually occurs. This must be of an artificial nature and the fact that the patients may have been up late the night before would be an influencing factor and there may be a resumption of normal basal temperature the next day. Consequently, it must be inevitable that mistakes will be made in interpreting temperature charts. It also must have a certain amount of physiological correlation, and that brings up some comment made by Dr. Hughes indicating the temperature rise due to progesterone. I think it has been fairly adequately proved from various sources that the rise in temperature is due to activity in the organism. I am sure he will be interested to learn that we have kept temperature charts on individuals who have had hysterectomies and a temperature rise occurs in patients with no uteri. So there is something else besides the action of the endometrium, but just what it is I do not know.

Dr. Pierson asked whether it is worth while pursuing this technique and using temperature charts on patients. I believe it is if there is an understanding of the limitation of the procedure.

Insofar as artificial insemination is concerned, it seems to me obvious from these findings, as well as many others, that it would be unwise to administer artificial insemination to a patient at the time of the temperature rise. It must be spread over a couple of days around the time of ovulation. Those taking the temperature charts must have a clear understanding of the variability of the temperature.

MEASUREMENT OF PAIN INTENSITY IN LABOR AND ITS PHYSIOLOGIC, NEUROLOGIC, AND PHARMACOLOGIC IMPLICATIONS*

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THAT labor is painful is generally acknowledged. Accurate information as to the neurology and physiology of parturition has been available for several hundred years. The pharmacology of pain relief is a modern development, having been introduced just over a century ago. Only recently have attempts been made to obtain quantitative measurements of pain intensity in labor,[1] so desirable for proper therapy.

Measurement of Pain Intensity in Labor

The measurements of pain intensity were first made before analgesia on 13 patients,[1] and subsequently on a total of 26 patients, of whom 19 were also studied after the administration of various analgesics.[2] These studies have been tedious and time consuming, involving observations at the bedside for long periods of time during the past three years.

The method of investigation has been previously described.[1, 2] The Hardy-Wolff-Goodell pain apparatus[3] or dolorimeter (Fig. 1) was employed to produce a thermal stimulus on the skin for a period of three seconds. The stimulus intensity causing a sensation of warmth, followed by the slightest noticeable pain was regarded as the "pain threshold." Twice this amount of stimulus causes the greatest perceivable pain or "ceiling pain" which is equivalent to 10½ dols.† This heat was sufficient to produce a third-degree burn. Therefore, the entire range of pain intensity was from threshold to 10½ dols, as determined by the number of millicalories of heat applied to the test area. The development of the pain scale has been presented elsewhere in more detail.[4, 5] During labor, measurements of pain threshold were made between contractions, and measurements of the actual pain intensity were usually made during or after the contraction. The results in millicalories are then interpolated on the scale as dols, giving the actual intensity of the labor pain.

The skin pain threshold does not vary during pregnancy, labor, or the puerperium; that is, the number of millicalories required to evoke threshold pain remains uniform. This is contrary to the often heard expression that a given patient has a "high" or "low" pain threshold.

Toward the end of pregnancy, the intermittent Braxton Hicks contractions are relatively painless, at which time there is little or no associated dilatation of the cervix. Uterine contractions produced by intravenous Pitocin, lasting 100 seconds, and occurring every 3 minutes are also relatively painless, unless the cervix is dilating. It is generally accepted that labor has begun when the cervix starts to dilate. As labor progresses the contractions appear to become more painful, reaching the severity of 3 to 4 dols, or the equivalent of menstrual

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†A dol is a unit of pain equal to one-tenth of the greatest painfulness. Ten dols are equal to a third-degree burn of the skin.

cramps. At this time, the average patient requests some analgesia. As labor continues, determined by the cervical dilatation, the pain intensity reaches 5 to 7 dols. Just before full dilatation of the cervix the pain intensity ranges from 8 to 10 dols.

During the second stage of labor, the pain intensity has been measured at 10½ dols, and the millicalories of heat necessary to reproduce the pain of the second stage produce a third-degree burn on the skin. This pain is chiefly due to the tissue damage associated with the dilatation and stretching of the lower vagina, vulva, and perineum. At this time, the patients' cries are usually loud and most of them appreciate anesthesia. Immediately post partum, the after-pains have an intensity of 3 to 4 dols, which may be due in part to the contractive closing of the cervix.

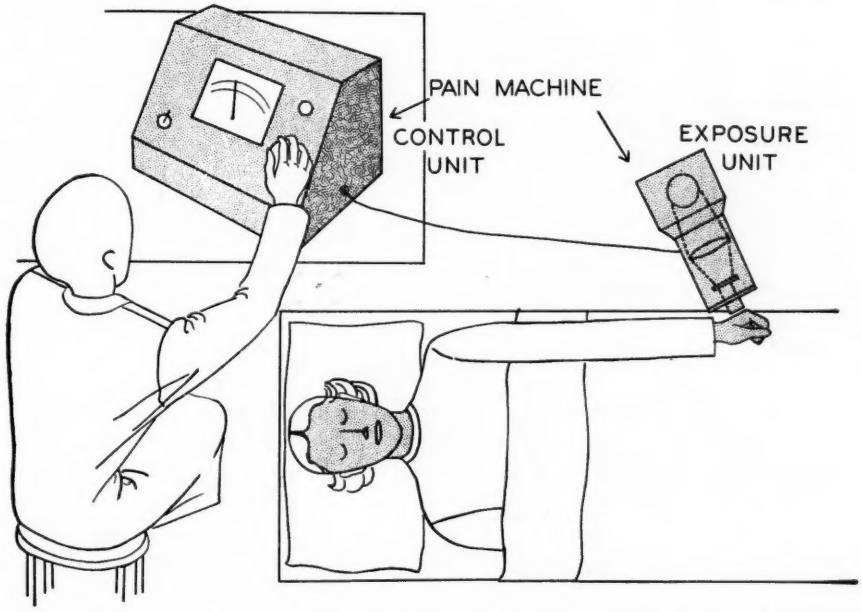

Fig. 1.—Diagram illustrating pain machine, or dolorimeter, in use. While exposure unit is held against dorsum of hand, we have found it preferable to use the forearm. Control unit varies thermal energy to produce necessary pain intensity.

Physiology of Pain in Labor

It is obvious that the labor pains coincide with the uterine contractions and it is only natural that the latter have been studied intensively by internal and external hysterography. There are relatively few studies on the dilatation of the cervix as the cause for the labor pains. However, the uterine contractions do not appear to be responsible for much of the pain in labor for the following reasons: (1) Pitocin-induced contractions are quite painless until the cervix begins to dilate; (2) Braxton Hicks contractions are also quite painless until the cervix begins to dilate; (3) uterine contractions during caudal anesthesia, which blocks the nerves going to the cervix but not those innervating the fundus, provoke little pain; (4) uterine contractions after presacral neurectomy are relatively painless.

It has been determined[6] that the average normal primipara requires 136 to 218 contractions to complete the first stage, while multiparas require a shorter number, namely 31 to 150, depending on when the membranes rupture. Primiparas require about twenty contractions in the second stage of labor, and multiparas ten pains on the average to effect delivery. These are ceiling pains, of 10½

dols' intensity. There are many variable factors that govern the number of contractions, and therefore the length of labor, aside from the uterus itself, such as the type of pelvis, position of the fetal head, the mechanism of labor, and the cervical resistance. It is generally stated that primiparas have an average total length of labor of eighteen hours, and multiparas have a duration of twelve hours. According to Föderl[41] the average duration is thirteen hours, and eight hours, respectively.

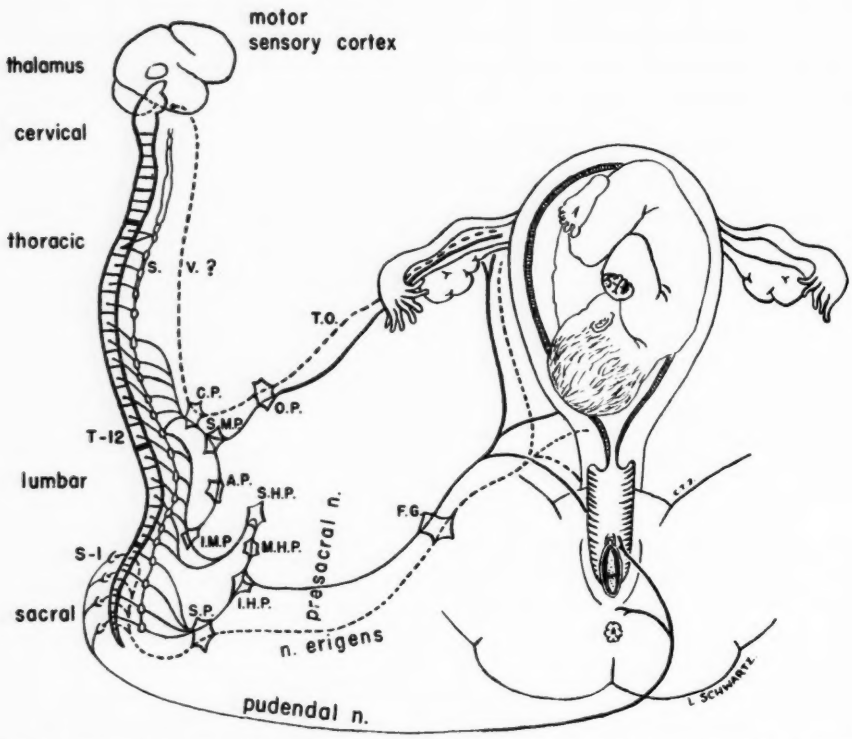

Fig. 2.—Schematic diagram of the innervation of the organs of parturition according to prevailing concepts (right side not shown).

Sympathetic system:

C. P., O. P., A. P., S. P.—Coeliac, ovarian, aortic and sacral plexuses.

S. M. P., I. M. P.—Superior and inferior mesenteric plexuses.

S. H. P., M. H. P., I. H. P.—Superior, middle, and inferior hypogastric plexuses (presacral nerves).

F. G.—Frankenhäuser's ganglia, which are bilateral although only one is shown.

Parasympathetic system (dotted lines):

V.—Vagus nerves which are bilateral although only one is shown.

n.—Erigens.

Allowing for individual patient variation, the pain intensity in dols is approximately equal to the dilatation of the cervix in centimeters. For example, when a number of patients have an average pain intensity of 6 dols, the cervix is about 6 cm. dilated. This gives a clue as to the chief origin of the pain in labor, namely the *dilatation of the cervix.* At times, this structure suffers tissue damage such as complete or partial detachment, lacerations, and sometimes does not dilate sufficiently so that Dührrsen's incisions are necessary. It is obvious that one could not experimentally dilate all of the pregnant cervices of obstetrical patients in order to study pain intensity. However, we did stretch the cervix slightly on several occasions at the time of sterile vaginal examination, provoking 6 to 8 dols of pain. Moreover, we have dilated the cervix of six gynecological patients and have elicited pain intensities varying from 6 to 8 dols.

Neurology of Pain in Labor

The autonomic and somatic innervation of the female organs of parturition have been described,[8-19] resulting in many views on the subject. The authors have summarized their interpretation of the innervation in Fig. 2.

It is not surprising that such an important organ as the uterus and cervix uteri has a *double,* bilateral autonomic innervation as follows: (1) presacral nerves passing through Frankenhäuser's ganglia on either side, and (2) tuboovarian plexuses in both infundibulopelvic ligaments. It has been shown[20] that either presacral neurectomy, bilateral infundibulopelvic resection, or both of these operations do not interfere with the normal emptying of the uterus. Presumably this is possible because the sacral (n. erigens) autonomics are left intact.

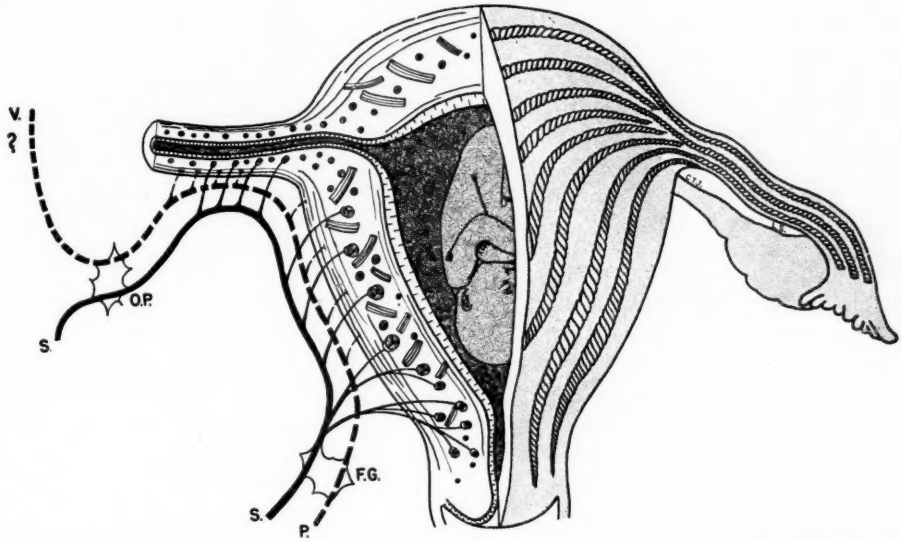

Fig. 3.—Diagram of the longitudinal and circular (and spiral) muscle fibers of the uterus and cervix, together with their probable innervation, which is bilateral although only one side is shown.

The pains of the first stage are virtually absent after presacral neurectomy.[44] We have made similar observations in three patients, one of whom had had two previous painful labors. Following neurectomy she had two additional labors with painless first stages. However, the second stage was very painful. This was eliminated in another patient by pudendal block.

Lesions of the spinal cord as high as C-7 do not interfere with the normal process of labor.[21-24] This may be due to the fact that the origin of the vagus nerves in the medulla remain intact. It has been suggested[10] but not generally accepted that the vagus sends fibers to the tuboovarian nerve, a view that seems reasonable from other considerations.

The autonomic nerves proceed along the course of the uterine vessels[25] and along the ovarian arteries as the case may be. There are ganglia on either side of the uterus in the broad ligaments.[25] Sensory corpuscles are especially numerous in the cervix[26] and only a few are found in the fundus. The uterus and cervix have longitudinal and circular muscle fibers in common with the Fallopian tubes, as one might expect from their Müllerian duct origin. Contractions initiated in the tubes spread over the uterus to the cervix.[13, 28] Present evidence makes it seem likely that the longitudinal muscle fibers are innervated by the parasympathetics, and the circular fibers by the sympathetics,

both receiving motor and sensory nerves as shown in Fig. 3. Von Basch and Hoffmann[27] advanced a theory in 1877 to the effect that the parasympathetics were excitatory to the longitudinal fibers of the fundus and cervix, and inhibitory to the circular fibers; and that the sympathetics were inhibitory to the longitudinal and excitatory to the circular muscle fibers. Whitehouse and Featherstone[28] arrived at a similar conclusion in 1923 after studying the human uterus at the time of cesarean section under lumbar spinal anesthesia, and the labors of rabbits having trauma to the spinal cord. The predominance of muscle fibers in the cervix has been questioned recently,[29] although most of this work was done on multiparas who may well have a relative reduction in the total amount of muscle tissue in the cervix because of an increase in connective tissue following repeated birth trauma.

Most of the pain in the first stage of labor is due to dilatation and stretching of the cervix. Externally, the nonpregnant cervix is relatively insensitive to pain, since it can be electrocoagulated with the Cameron cauterodyne with little discomfort to the patient, even though a third-degree burn is inflicted. A similar stimulus on the skin evokes a 10½-dol pain, and causes a third-degree burn. This difference in pain sensation suggests a difference in the nature of skin and visceral pain. Obviously, it has not been practicable to study pain threshold and intensity on the cervices of the obstetrical patients, whereas techniques are available for use on the skin.[1-5] For this reason the skin was selected as the most convenient and practicable site on which to reproduce thermal stimuli for comparison with the labor pains. It has been shown[30] that electrical stimulation inside the uterus does not elicit pain.

Dilatation of the cervix is very painful in pregnancy.[31] We have gently dilated the cervix in several obstetrical and gynecological patients without anesthesia and provoked pain ranging from 6 to 8 dols. Theobald[36] produced a similar pain by placing a silver nitrate stick in the cervical canal. The pain in these experiments is referred to the lumbosacral area following the course of the first lumbar nerve so that local injection of the ilio-inguinal and iliohypogastric nerves relieves the pain.[37] Massage of the area is fairly effectual in relieving the pain during labor.

The question of uterine versus cervical origin of pain was investigated further in a patient at the time of cesarean section. The abdominal wall was opened in layers under local infiltration of 1 per cent procaine, without preliminary analgesia or anesthesia. Forceful palpation of all of the upper uterine surfaces failed to elicit pain. The patient was fully conscious and was carefully questioned and observed. When the lower uterine segment and cervix and bladder were palpated with force, sufficient pain was elicited to make the patient exclaim and writhe on the operating table. The vesicouterine fold of peritoneum was then incised transversely after infiltration with procaine. A midline incision was then made into the uterus, which was extended upward with the bandage scissors with virtually no pain, Extension toward the cervix was very painful. After delivery of the child, the placenta was separated manually from its attachment to the upper anterior fundus without pain. Insertion of the hand into the cervix produced considerable pain.

From the foregoing it is concluded that neither electrical nor mechanical stimulation of the body of the uterus is painful, while forceful dilatation of the cervix by the uterine contractions is very painful.

Let us now consider the causes of pain in the second stage of labor. Since the upper vagina balloons out so readily in the knee-chest position, it seems likely that it dilates easily without much pain as the head enters the vagina. However, the vagina tapers forward toward the vulva and perineum becoming quite narrow so that dilatation and stretching of the vulva and perineum by

the crowning head provoke the severest pain of labor. This is largely due to tissue damage of an area supplied by the somatic sensory innervation composed of pudendal nerves, as shown in Figs. 2, 4, and 5.

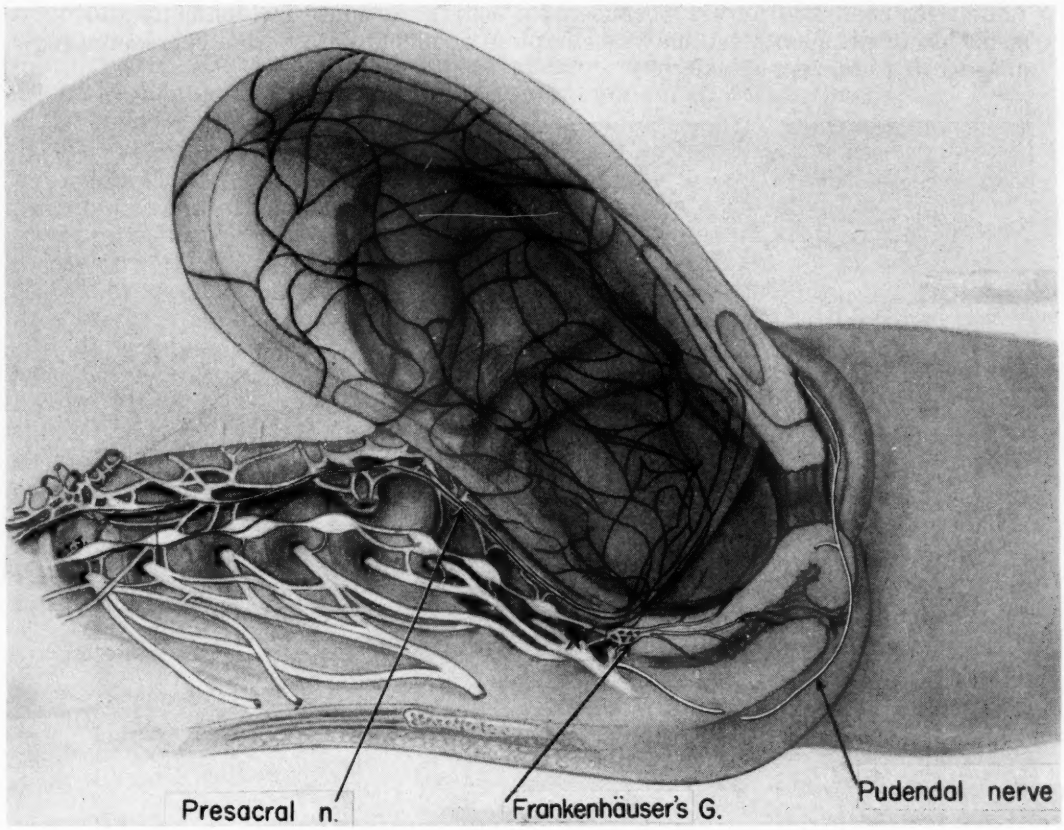

Fig. 4.—The autonomic innervation of the uterus and cervix is affected by morphine, heroin, Demerol, etc. The somatic sensory nerves can be affected by local procaine infiltration, pudendal nerve block, or low spinal anesthesia.

Pharmacology of Pain in Labor

The study of the analgesic effects on pain intensity of actual patients during labor represents an advance in pharmacology. Any discussion of pain intensity in labor requires a knowledge of the complex neurophysiology of the organs of parturition including (a) the higher consciousness (cerebral cortex), (b) the thalamus and medulla, (c) the spinal cord, (d) the autonomic nervous system, (e) the peripheral somatic nerves of the perineum, (f) the plexuses, ganglia, synapses, and end organs. Moreover, a knowledge is necessary of the pharmacologic action of the various amnesic, hypnotic, analgesic, and anesthetic drugs employed in obstetrics to alleviate the pains of labor. No single agent is likely to be suitable because of the differences in the innervation responsible for the pain in the first and second stages of labor. Therefore, several agents or techniques are generally employed as the labor progresses. At first a small dose of a barbiturate suffices, then morphine and scopolamine or Demerol, repeated perhaps during the first stage; followed by local infiltration, pudendal block, caudal, or spinal anesthesia, or inhalation anesthesia for the second stage and the delivery.

A. The Cerebral Cortex.—

The higher consciousness plays a primary part in pain perception which is either lost during periods of unconsciousness, i.e., after ether anesthesia, or decreased after the administration of certain drugs such as morphine, scopolamine, Demerol, and heroin because of a central action. Detachment and dissociation or disorientation may be complete or incomplete with a corresponding absence or reduction of pain.

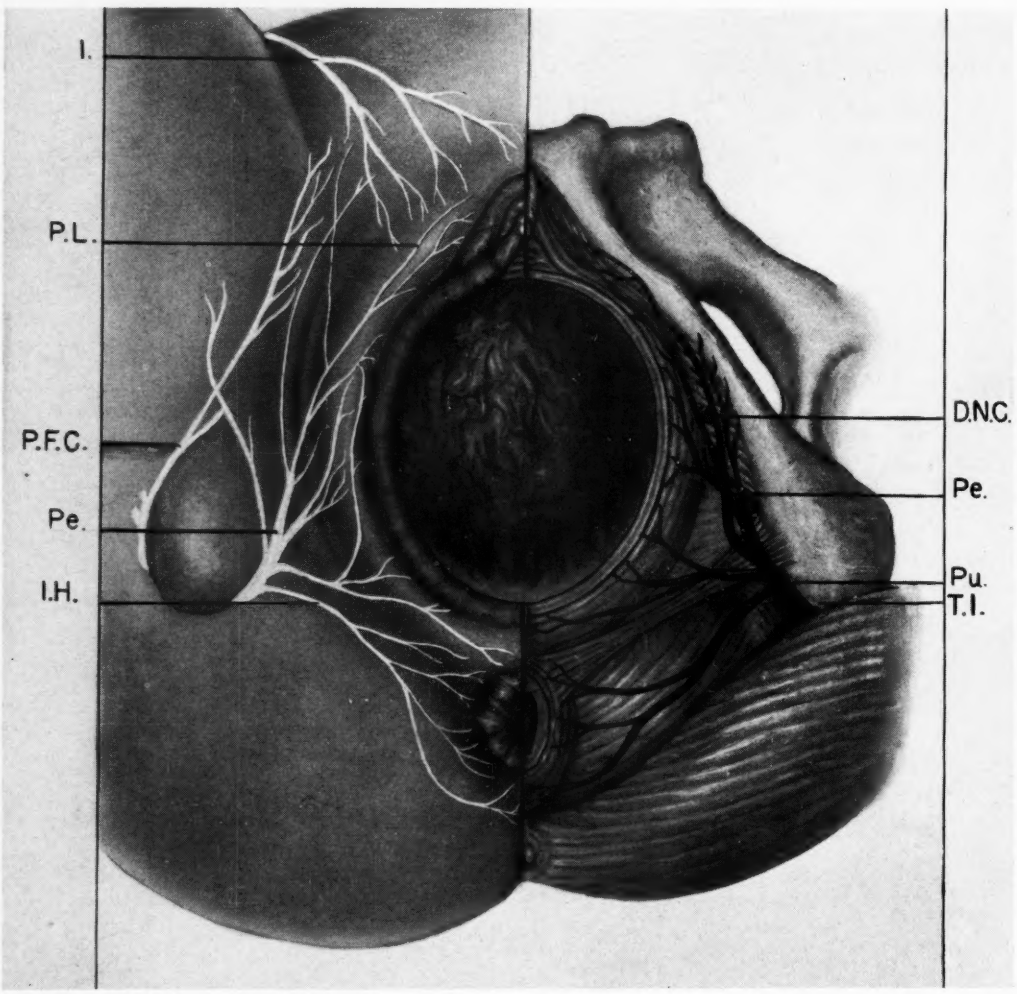

Fig. 5.—Schematic diagram of the somatic, motor, and sensory innervation of the vulva and perineum which lends itself so readily to local infiltration or pudendal nerve block.

The unmedicated patient, when awake, has a definite reaction pattern to the labor manifested by varying degrees of apprehension, anxiety, and fear. This is less marked in most multiparas who have experienced labor. Some patients become quite agitated and others are quite stoic. This has been correlated with expressions regarding "low pain threshold," and a "high pain threshold." Nevertheless, the reaction pattern has often been the sole clinical guide as to the amount of pain experienced in labor. It has provided much of the basis for obstetrical opinion regarding the efficacy of certain analgesics

as well as the various methods of psychological control of labor including suggestion, hypnosis, and, more recently, "natural childbirth."[32-35] Now that quantitative methods are available for measurements of pain intensity, they have been employed in a study of the common analgesic agents employed in obstetrics.[2] A typical decrease in pain intensity after the administration of morphine and scopolamine is shown in Fig. 6. These drugs also improve the reaction pattern. There were more smiles, greater equanimity, and decreased fear after the analgesic injections, with a minimum of effort on the part of the patient, nurse, and obstetrician.

Preparation for "natural childbirth" entails much antepartum instruction as to the physiology of pregnancy, exercises to produce relaxation during pregnancy, and other orientation lectures and visits to the labor and delivery rooms, and has been useful.[32-34] Other pyschic activity has been recommended to distract the patient during labor, such as knitting, towel pulling, music, television, and conversation, and they are of some value as is the actual presence of the obstetrician.

Ten patients were prepared for "natural childbirth" in order to ascertain whether this extensive preparation had any effect on the pain intensity during labor. Two developed pre-eclampsia and were excluded from the studies. Six were studied in labor and they had about as much pain as the control patients; of this number, five requested analgesia and anesthesia, and one, a multipara, did not ask for any medication. During the period without analgesia, these patients appeared to be at ease, did not cry or groan, and were as well composed as the nineteen control patients who received analgesia.[2] However, most of the patients expressed themselves as having been deceived as to the amount and intensity of pain to expect in labor.

It occurs to us that there are indications for "natural childbirth" as well as contraindications. The latter occur in about 15 per cent of cases in an obstetrical practice, and in this group of patients with toxemia, cardiac disease, hypertension, contracted pelvis, prolonged labor, abnormal presentation, placenta previa, etc., analgesia and anesthesia play an important role in the proper management. Several of our patients developed such complications for which they had not been prepared by their course in "natural childbirth," and they were totally unnerved by the turn of events away from the expected pattern. It would appear that a program of indoctrination, to be entirely successful, must also prepare the patient for all complications.

B. Thalamus and Medulla.—

The action of analgesia and anesthesia on the thalamus and medulla is generally that of disorganization and so-called depression. It is difficult to form an opinion as to action on various motor and sensory centers in the cortex and medulla, since much of it is associated with the cortical activity already discussed. It is known that morphine constricts the pupil, and depresses the respiratory center. The former is regarded as a central parasympathetic action on the longitudinal muscles of the iris. Apomorphine stimulates the vomiting center. General anesthesia, as with ether and chloroform, will stop the labor completely, evidently because of a central action of these agents.

C. Spinal Cord.—

Labor must be regarded as an intrinsic act, since uterine contractions can occur in patients with spinal-cord lesions[20-23] in whom the cervical dilatation is relatively painless. Temporarily, a similar situation can be produced by the use of caudal and spinal anesthesia as indicated in Fig. 2. Unfortunately, these techniques interfere with the perineal reflex so that the urge to bear down is decreased or absent, resulting in a greater incidence of forceps deliveries, which are not difficult because of the greater muscular relaxation.

They are ideal for delivery of the aftercoming head in a breech presentation. During spinal anesthesia, the uterine contractions are virtually painless, perhaps 1 to 2 dols in severity.

Most analgesics have some stimulating effects. Morphine, for example, stimulates the peripheral parasympathetics supplying the longitudinal muscle fibers serving to dilate the cervix, which is opposite to the constricting action observed in the eye.

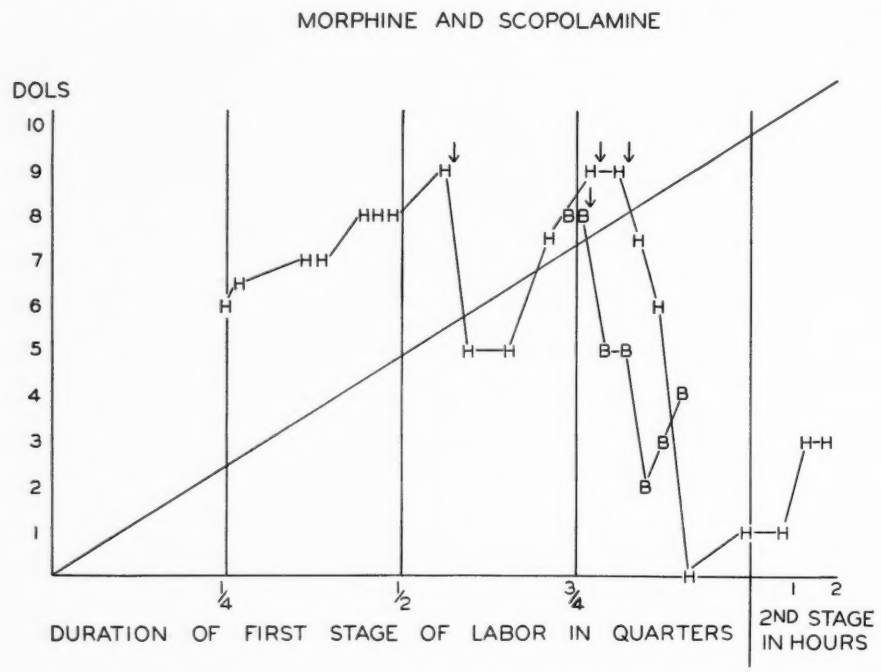

Fig. 6.—Showing how the pain intensity of two patients in the first stage of labor was lowered by morphine, 0.015 Gm., and scopolamine, 0.0004 Gm. Each arrow indicates an injection of both these agents.

The use of morphine, Demerol and heroin in labor is followed by a reduction in uterine activity and pain intensity, which is often interpreted by the obstetrician as a slowing of labor. Actually, this is not always the case since most reports give the average duration of labor in primiparas as twelve to thirteen hours, and eight to nine hours for multiparas, indicating that the cervix dilates as fast after analgesia as before, despite the apparent lessening of uterine activity. Föderl[41] reports similar average durations of labor in his large series of patients. From our own unpublished study of patients receiving morphine and scopolamine analgesia with and without rectal ether, it was readily apparent that patients with long labors received more analgesia rather than that analgesia per se was the cause of the long labors.

D. Autonomic Nervous System.—

The action of morphine and other analgesics on the sympathetic and parasympathetic systems of the organs of parturition is not completely understood. There is evidence that a reduction of uterine activity follows their administration, which is accompanied by a lessening of the pain. Whether there is a primary action along the nerve fibers and plexuses or on the end receptors has not been determined in labor. A slowing action is observed in isolated muscle strips in the laboratory after many of the obstetrical analgesics, indicating

action on the end receptors rather than on the sympathetic and parasympathetic chains per se.

Labor is associated with a flushed face, profuse sweating, and moist palms, which are of autonomic origin. These symptoms virtually disappear after an injection of morphine, morphine and scopolamine, heroin, or morphine and Demerol. Again, it is difficult to exclude a central rather than a peripheral action on the autonomic nervous system.

E. Peripheral Somatic Nerves.—

The pain intensity in the second stage of labor reaches 10½ and is due largely to the dilatation and stretching of the vulva and perineum, supplied by the muscular and sensory branches of the pudendal nerves on either side. It is possible to control this pain with local procaine infiltration and episiotomy. Pudendal nerve block also relieves it, as does a low spinal or caudal anesthesia. The number of perineal pains may vary from ten to fifty and at this time even doctor-mothers were most grateful for anesthesia.[42]

F. Plexuses, Ganglia, Synapses, and End Organs.—

The action of the various obstetrical analgesic and anesthetic agents on these structures in the various organs of parturition have not been well established. Some action can be demonstrated in isolated human uterine muscle-strip experiments in vitro. Curare, for example, stops the contractions of the uterine muscle.

Comment

From the foregoing discussion, the search for an ideal obstetrical analgesic may never materialize because of the complex neuromuscular mechanism of the first and second stages of labor. Pain in the first stage of labor is due to cervical dilatation and the stimuli are carried by the autonomic nervous system, while in the second stage it is due to perineal dilatation and is carried by somatic sensory pudendal nerves. No single analgesic agent or technique is available at present easily to meet the requirements of a complete labor.

The ideal analgesic in the first stage of labor is one that is capable of reducing the pain intensity from 6 to 8 dols to 1 to 2 dols; of raising the pain threshold several dols, having a low toxicity for both mother and child; and of producing no undesirable side effects such as hyperexcitation or unconsciousness, so that the patient is able to help herself. The drugs approaching this ideal are heroin, morphine and Demerol, and morphine and scopolamine, in that order. If a general anesthesia is used in the second stage these analgesics serve as a very satisfactory preanesthetic medication by eliminating the excitement phase of the induction and by drying up some of the nasopharyngeal secretions. This cannot be accomplished by "natural childbirth," and these patients, unless medicated, have a poor induction. Analgesic medication also quiets the patient for delivery under local anesthesia, infiltration with procaine, or for pudendal nerve block, caudal and low spinal anesthesia. This permits the patient to be awake, to see the delivery, and otherwise to experience the full thrill of having a child as painlessly as possible.

Finally, it may be concluded that the pain intensity of labor can be measured by quantitative means using the dolorimeter.[3] These studies have led us to realize that the uterine contractions per se are relatively painless, and that most of the pain in the first stage of labor is due to the dilatation, stretching, and tearing of the cervix. Most obstetrical analgesics reduce uterine activity without slowing the cervical dilatation.[49] There is a concomitant relief of pain probably because of a central and peripheral action of these agents rather than any direct action on the uterus. Adair and Pearl[46] studied the postpartum uterus with internal hysterography and observed that morphine produced very

little effect on the tone and activity of the uterus. However, scopolamine tended to relax the uterus and prolong the contraction interval, and increase the amplitude of the contractions. On the other hand, our experiences with apomorphine indicate a profound slowing of uterine activity. The pains can be relieved by sacral anesthesia,[17, 44] which also serves to decrease the magnitude of the uterine contractions, as do the various analgesics such as morphine, heroin, and Demerol and scopolamine, which also have a peripheral action on the cord and its autonomic nerves.

With regard to the second stage of labor, most of the pain appears to be due to tissue damage, as indicated by the marked stretching, tearing, and dilatation of the vulva and perineum, rather than to the uterine contractions per se. Pudendal nerve block and/or local procaine infiltration eliminate most of this pain; meanwhile the uterine contractions produce only slight pain in the vicinity of 2 to 3 dols.

Summary and Conclusions

1. The quantitative measurement of pain intensity in labor can be measured with the Hardy-Wolff-Goodell dolorimeter. The visceral pain occurring concomitant with the uterine contractions can be satisfactorily compared with a test pain on the skin.

2. Apparently, the uterus has a double bilateral innervation through Frankenhäuser ganglia and the tuboovarian nerves on both sides. Evidently the sympathetics provide motor and sensory nerves to the circular muscle fibers of the uterus and cervix, and the longitudinal muscle fibers receive their motor and sensory innervation from the parasympathetics or the craniosacral portion of the autonomic nervous system.

3. The pain in the first stage varies from 0 to 10 dols and is largely due to stretching and dilatation of the cervix. The sensory impulses can be controlled by drugs and techniques which slow the uterine contractions. Heroin, morphine and Demerol, and morphine and scopolamine are valuable in approximately that order of effectiveness. They have an action on the central and autonomic nervous systems.

4. Pain in the second stage of labor has an intensity of 10½ dols and is largely due to the stretching and dilatation of the vulva and perineum supplied by somatic sensory nerves. It can be controlled by pudendal block, sacral and caudal anesthesis, or by the general anesthetics.

5. The regimen known as "natural childbirth" has little if any effect on the pain intensity in labor. However, it does produce a satisfactory reaction pattern in the patient comparable to that obtained with moderate doses of heroin, morphine and Demerol, and morphine and scopolamine, in contrast to that of unprepared or unmedicated patients. This method of psychological control of labor governs the reaction pattern, but does not decrease the actual pain experience by the patient.

6. Because of the complex physiologic, neurologic, and pharmacologic aspects of the first and second stages of labor, a combination of analgesic and anesthetic drugs and techniques seems to give the best results, rather than any single agent or method. The mode of action of these various obstetrical analgesics is both central and peripheral.

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THE RELATIONSHIP OF DISORDERS OF THE BLOOD-CLOTTING MECHANISM TO TOXEMIA OF PREGNANCY AND THE VALUE OF HEPARIN IN THERAPY

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THIRTY years ago, Abderhalden[1] introduced in his "abwehrfermente" theory the concept that protective ferments developed in the serum of the mother in response to the invasive action of the placenta. Although there were a number of reports both in favor of and against this theory, the consensus at that time agreed with Van Slyke[44] that nearly all human serum could digest coagulated protein at least to some extent when it was incubated with placental tissue as advised by Abderhalden, and that the test was not specific for pregnancy.

A few years later, however, Hofbauer[15] discovered that the placenta produced both a coagulant and a proteolytic enzyme, and that there was a demonstrable rise in the antitrypsin titer of the blood in pregnancy. This titer was found to be high in eclampsia. Although both of these enzymes could be found in other organs, Hofbauer[8] believed that only the placenta could easily liberate them into the blood stream, and that deleterious effects occurred when the quantity of enzyme absorbed was sufficiently large to overwhelm the anticoagulant and antiproteolytic defense mechanisms of the body. He believed that the coagulant enzyme damaged the cells of the kidney and liver, but he did not elucidate the part played by the proteolytic enzyme.

At about this same time, Obata[28] made a most significant experimental contribution to this problem. He noted that sublethal doses of placental extract increased the blood coagulability after injection into experimental animals and that, following injection of a lethal dose, the coagulability was decreased so that the blood would not clot. Pathological examination of these animals revealed degenerative cellular changes and platelet thrombosis in the lungs, liver, and kidneys, as well as areas of hemorrhage. These changes were similar to those found earlier by Schmorl[35] in his study of the pathology of eclampsia. In another phase of his study, Obata was able to neutralize the lethal effects of the placental toxin by addition of normal human serum; but, on the other hand, the toxin could not be neutralized if the serum of an eclamptic patient was used. In essence Obata's study indicated that eclampsia was due to a deficiency, in the mother, of a neutralizing substance for the placental toxin. Obata's findings were confirmed by Hayashi[14] and later by Dieckman.[9] In addition, Dieckman observed that pre-eclamptic serum could only partially neutralize the placental toxin.

Heparin in the form of "Liquaemin" was supplied through the courtesy of Dr. K. W. Thompson of Roche-Organon, Inc.

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In the past few years, G. S. and O. W. Smith[38] have brought forth evidence to support a toxin theory for the etiology of toxemia; according to their views there is a withdrawal of hormonal support from the uterus either during menstruation or with toxemia of pregnancy which results in an increased local tissue catabolism and the formation of a toxin which is absorbed into the systemic circulation. The toxin, which is immunologically similar to Menkin's "necrosin," is lethal to animals, hastens the clotting of blood, and has fibrinolytic activity.[39] As evidence for a systemic invasion by the toxin, fibrinolytic activity was observed in the blood during menstruation and in some cases of toxemia.[41] Willson and Munnell[50] also found evidence of fibrinolysins in toxemia. The Smiths have found a factor in the pseudoglobulin fraction of menstrual discharge and in all materials containing the toxin and fibrinolytic enzyme which protects rats against lethal doses of the toxin.[40] They treated several cases of toxemia with this substance, and some, though not all, of these cases improved clinically. When improvement occurred there was noted a diminution in the fibrinolytic activity of the blood.[42]

In 1947, Schneider[36] presented convincing evidence that the toxic factor in placental extracts in thromboplastin, and that the toxic substance derived from progestational mucosa is also thromboplastin.[37] He was able to protect mice from the lethal action of placental toxin by mixing the extract with heparin or previously injecting the animal with heparin. Accordingly, Schneider suggested that thromboplastin is indeed the toxic substance in the placenta which is primarily responsible for toxemia of pregnancy and that heparin should be effective in treatment.

A hypothesis to explain this mechanism for the elaboration of the placental toxin in toxemia of pregnancy has been presented by E. W. Page.[30, 31] He suggested that the initiating factor is placental ischemia which results in anoxia and injury to the cells of the trophoblast. As a result of the catabolic processes thus initiated, active proteins are liberated into the maternal system. These proteins, one of which may be thromboplastin, could produce the systemic lesions and the clinical symptoms of toxemia of pregnancy.

Blood Coagulation and Heparin in the Elucidation of the Theories of Toxemia of Pregnancy

The blood clotting phenomenon is initiated by thromboplastin after it has been liberated from cells or platelets by mechanical injury or by the action of a platelet lysin. Schneider's report suggests that thromboplastin may also be introduced directly into the blood stream of the mother from the placenta. The amount made available would be greatest in toxemia of pregnancy. In any event, free thromboplastin in the presence of calcium activates the enzymatic conversion of prothrombin into thrombin, and the thrombin thus formed catalyzes the formation of fibrin from fibrinogen. Fibrin forms the clot.

Besides a coagulant system in the blood, there is also a fibrinolysin system which has been previously referred to by a variety of terms. The active principle of this system has been called plasma trypsin[11] and plasmin.[5, 16] Loomis, George, and Ryder[25] in a recent report have suggested that the active enzyme be called fibrinolysin, its precursor, profibrinolysin, and the respective inhibitors, antifibrinolysin and antiprofibrinolysin. Fibrinolysin is a euglobulin which is water insoluble but saline soluble. It is capable of destroying fibrinogen and prothrombin, but thrombin seems to be immune to its lytic action. Fibrinolysin is derived from profibrinolysin when the latter is activated, but this conversion is normally inhibited by the overneutralization of the inhibitor, antiprofibrinolysin. If fibrinolysin is formed, antifibrinolysin is available to block its action. The inhibitors are resident in the albumin fraction and normally prevent both the formation and the action of fibrinolysin.

Serious consequences may occur if the active enzymes of these two systems are released. Thromboplastin produces intravascular clotting. Fibrinolysin initiates clotting and may then destroy fibrin and fibrinogen to produce uncoagulable blood. Agents are, however, becoming available to prevent these reactions.

Heparin when administered in proper amounts may prevent the action of thromboplastin,[4] and it has been used extensively in man for that purpose.[23, 33, 46] The fibrinolysin system can be experimentally antagonized in vitro with crystalline soybean trypsin-inhibitor,[21, 22] and heparin also has a certain amount of antitryptic action in vitro.[16, 34]

For purpose of discussion a composite hypothesis can be developed from the preceding information. The placental cells contain substances which are either active coagulant and fibrinolytic enzymes or they are activators of these systems. These enzymes may be liberated from the placental cells and gain entrance into the circulation when there is placental anoxia or a withdrawal of hormonal support. They are immediately neutralized by respective specific inhibitors and no systemic effect may occur. But if there is a great quantity of exogenous enzyme gaining entrance into the maternal circulation, or if the quantity of specific inhibitors is reduced, the blood clotting and fibrinolytic systems become active. There will be then increased blood coagulation and thrombosis. The fibrinolytic system may first increase the clotting tendency and then decrease it by destroying fibrinogen. It may produce hemorrhages and various cytotoxic effects. Plasma from such patients will be unable to neutralize the lethal action of placental extracts since the inhibitors have been destroyed.

Such a hypothesis suggests that for therapy it is necessary to remove the placenta since it is the source of the enzymes, to restore better placental function by correcting anoxia or replenishing hormonal support, or to administer specific inhibitors for both the coagulant and fibrinolysin systems. It is well known that removal of the placenta is the most effective way to treat toxemia, but in so doing it may be necessary to sacrifice the fetus. Hormone administration has been effective in preventing toxemia.[38] Attempts at neutralizing the toxins have been few and experimental. Protective pseudoglobulin is said to have produced improvement in some cases of toxemia.[38] Attempts have been made to treat toxemia with heparin and both favorable and unfavorable results have been reported.[3, 27, 32] If heparin cures toxemia of pregnancy, the theory that toxemia is due to a placental toxin which is thromboplastin is then established. If it does not, this fact would stand as strong evidence against the acceptance of this theory. Thus, the use of heparin in the treatment of toxemia may not only give us a means of therapy but also prove or disprove the thromboplastin hypothesis.

Clinical Reports on the Use of Heparin in the Treatment of Toxemia

Maeck and Zilliacus[27] treated one pre-eclamptic patient at the Woman's Hospital in New York City and referred briefly to three other cases treated under their direction in the University Obstetrical Clinic in Helsinki, Finland. The case they reported in detail may be briefly summarized. A 33-year-old, white primipara was admitted to the hospital in the seventh month of pregnancy because of vaginal bleeding and moderately severe toxemia. With magnesium sulfate, hypertonic glucose, and sedation, the toxemia subsided over a six-day period and the patient was followed in the clinic. Twenty-four days later, she was readmitted to the hospital with an exacerbation of her toxemia, similar in severity to the first admission. She was treated with magnesium sulfate and hypertonic glucose as on the first admission, and in addition she received an infusion of 5 per cent glucose which contained 150 mg. heparin.

The toxemia subsided and the patient was delivered of a 1,650 gram infant eighteen days later. The blood pressure and albuminuria were compared graphically for the two admissions and the authors believed that these curves demonstrated a more rapid clearing of the toxemia on the second admission. This they attributed to the heparin. All three of the cases treated in Finland were post partum, and the results in two were equivocal.

E. W. Page[32] briefly reported four cases of toxemia treated with heparin. These cases after adequate control periods received heparin for seventy-two hours. The heparin was administered by continuous infusion in two, and by intermittent injection in two cases. In the two mild patients, hypertension and albuminuria cleared quickly. In one of the severe cases, there was no improvement; but in the other, hypertension and proteinuria decreased. The toxemia, however, became worse twelve hours after heparin was stopped, and the pregnancy was terminated by cesarean section.

Barnes[2] has treated four cases of toxemia experimentally with heparin. Three cases received adequate amounts of heparin, and in these three there was no definite sign of improvement in the toxemia due to the heparin. One patient developed convulsions while being treated with heparin.

It is apparent, when these reports are analyzed critically, that there is not a single case of toxemia in the literature which can be said to have been definitely improved by heparin therapy alone.

Clinical Trial of Heparin in the Treatment of Toxemia

The four cases presented were selected from clinic patients who were admitted to the abnormal obstetrical wards of the Sloane Hospital during a period of one year, 1947. Cases 2, 3, and 4 were the most severe examples of toxemia admitted during this period in which adequate control periods and kidney function tests could be done. The control period consisted of at least seventy-two hours immediately following admission during which time the patient was placed on a low salt diet, kept at bed rest, and received no form of medication. An accurate fluid balance was maintained and all urine specimens were examined for protein. The body weight was determined daily under standard conditions. Blood studies were done every two to four days to follow changes in hematocrit, nonprotein nitrogen, uric acid, and serum protein.

In order to classify the severe cases of toxemia, renal function studies were performed with inulin and sodium para-aminohippurate* during the control period and again after delivery. Water retention studies were also carried out during the control period and again after delivery. In this test, the amount of urine excreted in four hours after the ingestion of one liter of water under standard conditions was determined. The results were then compared with normal controls. This study was based upon the water diuresis test described by Janney and Walker.[18]

The blood coagulation time was determined by a modification of the method described by Wiener and Shapiro.[49] A machine was developed which rotated six 25-milliliter flasks simultaneously at one revolution per minute in a temperature-controlled water bath. The fixation of the clot to the flask wall was the end point. It was readily visualized through the glass-walled water bath. This method permitted control of two important phases of blood clotting: agitation and temperature. With the six flasks it was possible to add blood to increasing concentrations of heparin and to study in vitro heparin tolerance. This was a modification of the procedure described by Waugh and Ruddick.[47] It gave some clue as to the susceptibility of the subject to heparin and as to the amount of heparin necessary to obtain a safe prolongation of

*Supplied through the courtesy of Dr. J. W. Crosson of Sharp & Dohme, Inc.

the clotting time. The rotation method permitted a rapid and an accurate determination of the blood-clotting in subjects with prolonged clotting times (over forty minutes) where the Lee and White[23] procedure was inaccurate and time consuming.

Case Reports

CASE 1.—Mrs. S. B. was a 34-year-old white patient, para i, gravida ii, admitted to the hospital at term because of the sudden development of epigastric pain, generalized edema, moderate hypertension (140/90), and proteinuria. During the three-day control period there was no significant improvement. Heparin was administered every three hours subcutaneously during the test period to maintain an adequate elevation of the clotting time (five times the normal by the Lee and White method). The first day, 230 mg. heparin were given; the second day, 210 mg.; and the third day, 105 mg. A total of 545 mg. heparin was given during the three-day period.

There was no significant decrease in hypertension or proteinuria during the period of therapy, but there was some subjective improvement. The patient stated without interrogation that epigastric pain and dizziness disappeared after the second injection of heparin. Heparin was stopped because the uterus became irritable. For the next seven days without specific therapy, there was no significant improvement. The patient then went into spontaneous labor and was delivered of a normal, term infant. Post partum, the blood pressure was normal one day after delivery, and the urine was free of protein by the ninth day.

CASE 2.—Mrs. I. K., a 35-year-old Greek woman, para i, gravida ii, was admitted to the hospital in the thirty-second week of her second pregnancy. There was no history of previous hypertension or kidney disease. She was followed in the clinic from the fourth month of her present pregnancy. Suddenly, in the seventh month, she developed edema and a severe headache. On admission to the hospital the blood pressure was 170/100. The eye grounds showed spasticity of the arterioles without hemorrhage or exudate. The liver edge although palpable was not tender. The fetal heart could be heard and the reflexes were hyperactive.

During the control period, there was slight subjective improvement, and there was a moderate diuresis. No lowering of hypertension or decrease in clinical edema occurred, and the proteinuria increased. While the normal pregnant patient at this stage of gestation excretes about 78 per cent of water ingested in four hours, this patient excreted only 43 per cent. Kidney function studies revealed only a depressed glomerular filtration rate which returned toward normal after delivery. This is a common finding in cases of preeclampsia reported in the literature.[6, 10, 19, 29, 43, 48] The uric acid was 3.3 mg./100 c.c. and the serum protein was 5.31 per cent. The urine contained as much as 4.0 Gm. protein per liter as well as abundant finely and coarsely granular casts.

The course of this patient has been summarized in Fig. 1. A total of 815 mg. heparin was administered, mostly by intermittent intravenous injections over a four-day test period. During this time, the blood would often not clot with the Lee and White method, but by the rotation method the clotting time was maintained at approximately seven minutes. The normal clotting time for this patient during the control period was two minutes and thirty seconds by this method.

The blood pressure charted in Fig. 1 was the average of five determinations taken each morning. There was considerable fluctuation during the remainder of each day which is not represented. Certainly, there was no significant drop in blood pressure until after delivery.

During the period of therapy, the weight gradually increased, the urine output decreased, and the proteinuria became progressively heavier. On the last day of treatment, November 13, the patient developed epigastric pain and vomited. The blood pressure again became elevated and it was thought that the patient was getting worse. It was decided

to discontinue the heparin. For the next thirty-two hours, the patient was given 50 c.c. of 50 per cent glucose every four hours intravenously and was heavily sedated. There followed an excellent diuresis, but the hypertension and proteinuria remained unchanged.

One week after discontinuing heparin, the patient was delivered of a 1,680 gram infant which died twenty-four hours after birth. Postmortem examination demonstrated no evidence of hemorrhage other than that usually found in premature infants who die. Following delivery, hypertension and proteinuria cleared quickly. Four months post partum, the blood pressure was normal, and the urine was free of protein.

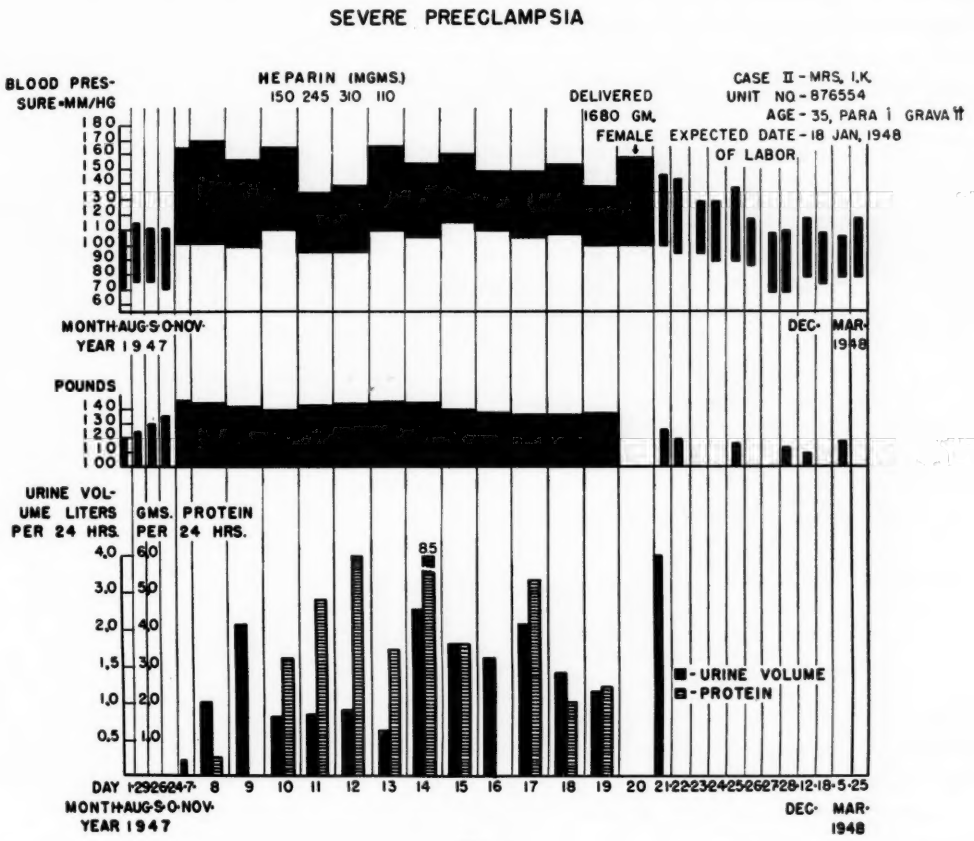

Fig. 1.

Case 3.—Mrs. M. M. was a 26-year-old Negro primipara. She gave no history of any serious illnesses, but her blood pressure was 118/90 three years before the present pregnancy. Her blood pressure was 125/85 in the fourth month of pregnancy, and there was no proteinuria. In the seventh month, the blood pressure rose to 142/98. One week later it was 180/114, and the patient was admitted to the hospital. She did not complain of headache, blurring of vision, or epigastric distress; but she had gained 6½ pounds in weight in one week. The retinal arterioles were narrow, but there was no hemorrhage or exudate in the fundi. There was moderate edema of the face, hands, and legs, and the reflexes were hyperactive. The uterus was the size of a seven months' pregnancy, and the fetal heart could be heard. The uric acid was 3.9 mg. per 100 c.c. and the serum protein was 5.41 per cent. The urine contained 3+ protein and occasional finely granular casts.

During the control period, three sharp rises in the blood pressure occurred, to as high as 210/125. It was necessary to administer hypertonic glucose and magnesium sulfate. After each injection, the blood pressure fell temporarily. Renal function studies demonstrated a

normal glomerular filtration rate, a lowered renal plasma flow, and an increase in the filtration fraction. These changes are typical of those found in toxemia of pregnancy complicated with hypertensive disease.[6, 7, 10, 19, 29]

Two thousand milligrams of heparin were administered over the seven-day test period, as presented in Fig. 2. The heparin was given by intravenous injections of 30 to 100 mg. every three to six hours. This produced a prolongation of the clotting time to the upper border of clinical safety. The blood would often not clot when tested by the Lee and White technique, but by the rotation method the clotting time was controlled between eight and ten minutes. During the period of treatment, there was no change in the patient's symptoms, except on the last day of treatment; in spite of excessive prolongation of the clotting time, the patient became drowsy and had a severe frontal headache.

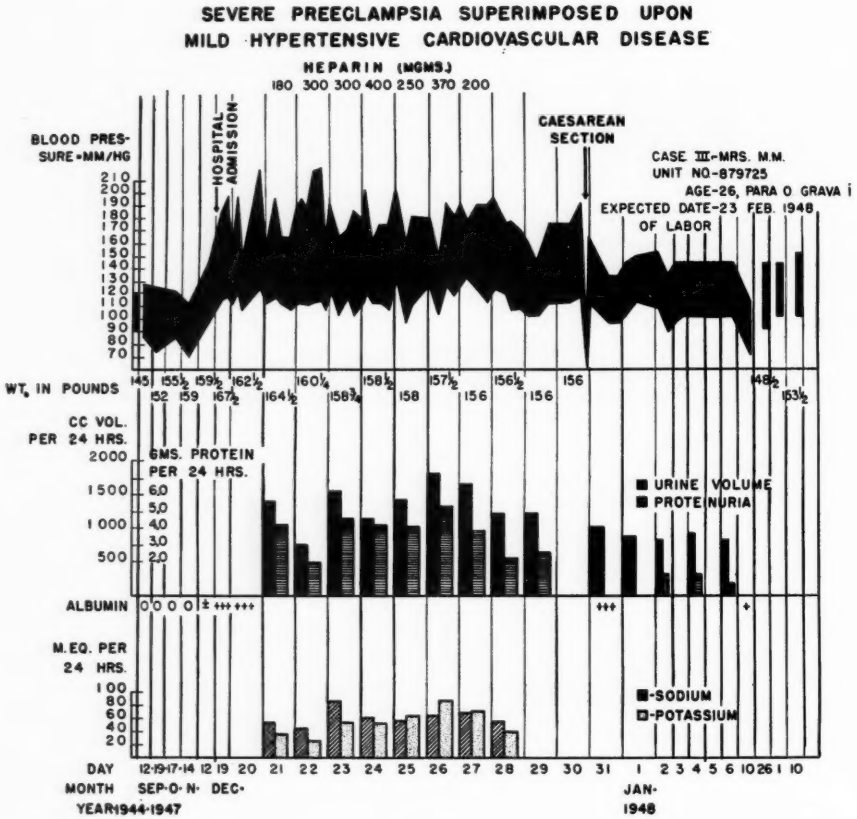

Fig. 2.

By inspection of the blood pressure curve presented in Fig. 2, several important observations can be made. The high diastolic blood pressure three years before this pregnancy indicated an underlying hypertensive tendency. There was considerable fluctuation of the blood pressure from hour to hour, but there was no definite trend toward lowering while on heparin. In striking contrast is the sustained drop following effective therapy, that is, delivery by cesarean section. The progressive rise in both diastolic and systolic blood pressure on follow-up indicates again the hypertensive tendency of this patient.

It was of importance that there was no excessive total weight gain during the pregnancy. The patient did, however, gain 8 pounds in the week preceding admission, but she lost 8½ pounds during the seven days of heparin therapy. This loss was accompanied by a reduction in clinical edema and it might be explained by the fact that the glomerular filtration rate was high.

The urine output was adequate and increased with the loss of weight and reduction of edema. The proteinuria varied directly with the urine output. From 3 to 5 grams of protein were excreted each day. Following delivery, there was no diuresis, but the proteinuria cleared quickly. Sodium and potassium excretion increased with urine output. There was little change in the relation of one to the other, although potassium excretion appeared to increase.

Notwithstanding having received large amounts of heparin and having an excessively prolonged clotting time, on the seventh day the blood pressure rose steadily, the patient became lethargic, and she complained of a severe frontal headache. It was admitted that heparin had failed to control her disease, and its use was discontinued. The patient was then heavily sedated; when there was no significant improvement in her condition after three days, a cesarean section was performed and a three-pound infant was delivered. As soon as the baby was extracted, the blood pressure fell to 90/60, but one hour later rose to 160/110. The infant was normal and survived.

Postoperatively, hypertension and proteinuria cleared rapidly, and eleven days later the blood pressure was 105/70. The urine contained 1+ protein. One year later, the blood pressure was 148/100, and the urine was free of protein.

CASE 4.—Mrs. M. L. was a 20-year-old para i, gravida ii, who had had a single immediate postpartum convulsion after her first term delivery. At that time the blood pressure was 150/110, the reflexes were very hyperactive, and the urine contained a heavy trace of protein. Fourteen days later the blood pressure was normal, and the urine was protein free.

In her second pregnancy she developed eclampsia at four and one-half month's gestation and was admitted to the hospital in a stuporous condition. The blood pressure was 174/120. There was spasm of the retinal arterioles. The tongue was swollen and lacerated; the neck, resistant; the liver, not tender. The fetal heart could be heard, but there was only slight pretibial edema. The nonprotein nitrogen was 44.3 mg./100 c.c., the uric acid was 4.6 mg./100 c.c., and the serum protein was 5.02 per cent. The urine contained 3.1 Gm. of protein per liter.

On bed rest, heavy sedation, and a salt-poor liquid diet the patient became gradually rational, her vision improved, and the urine output remained good. But even after the ninth hospital day there was no improvement in hypertension, proteinuria, or retinal arteriole spasm; and it was decided to try a course of heparin.

Three hours after the first intravenous injection of 50 mg. heparin, the blood would not clot by the Lee and White technique although the clotting time was normal just before the heparin had been given. Further administration of heparin was done with caution. Thus, 150 mg. heparin produced a persistent anticoagulant effect for over forty-eight hours.

During this period of heparin treatment, there was no clinical improvement. The average blood pressure just before treatment was 168/120; and the day following its conclusion, the pressure was 170/125. There was no clearing of proteinuria or increase in the urine output. Ecchymotic areas did appear around injection sites and where tourniquets had been applied. The retinal hemorrhages did not increase in size or number. The patient became more lethargic and heparin was stopped because there had been no improvement, and there was also the fear that a cerebral hemorrhage might occur.

Twelve days after admission or two days following the period of heparin treatment, the patient was delivered of an eighteen weeks' size, slightly macerated, stillborn male fetus. The placenta, which was easily expressed, weighed 105 grams. It was 10 cm. in diameter and exhibited multiple areas of infarction, the largest of which was 4 cm. in diameter.

Following delivery, there was rapid clearing of the toxemia. The blood pressure dropped immediately and remained around 120/80. The proteinuria cleared promptly. Renal function studies performed four days before and four days after delivery demonstrated a great reduction in both glomerular filtration and renal plasma flow comparable in degree with that found in chronic nephritis.

Comment

In this study, heparin was not an effective therapeutic agent in the treatment of four cases of toxemia of pregnancy. Three of these cases were selected because of their severity. This result does not support the contention of Schneider[36] that thromboplastin is the etiological factor in toxemia. It is also evidence against the preliminary suggestions by Maeck and Zilliacus[27] and by Page[32] that heparin is helpful in the treatment of toxemia, but it is in accord with the study by Barnes,[2] who also found that heparin was not effective in treatment of toxemia. Critically considered, there is no evidence in the literature that heparin is effective in the treatment of toxemia of pregnancy. Our observation that there was no improvement in these cases which could be ascribed to the heparin therapy convinced us that further clinical trial with this drug was not warranted.

The failure of heparin in these instances has no bearing upon the possible function of the fibrinolytic system in toxemia of pregnancy. Although heparin has been reported to have antitryptic action in vitro,[16] this action was found to be negligible in in vivo experiments. Horwitt[17] points out that 4 mg. of heparin have no more inhibiting power than 0.1 ml. of ordinary serum, and Ferguson[12] believes that unphysiological amounts of heparin would be required to produce systemic antitryptic effects.

Work is in progress in our laboratory on the fibrinolytic phase of the problem and this will be reported in a later article. Papers by O. W. Smith[41] and Willson and Munnell[50] have pointed out that there is fibrinolytic activity in the blood during menstruation, in toxemia of pregnancy, and after prolonged labors. Although not suggested in their writings, this fibrinolytic activity is most likely due to a disturbance in the fibrinolytic enzyme system normally present in the blood. This system when fully activated can destroy all of the body fibrinogen and probably much of the other plasma proteins in a few minutes,[24] and activation of this system could explain the reports in the literature that in some cases of eclampsia, the clotting time becomes prolonged, while just before death the blood may not clot at all. When the clotting mechanism is thus deranged, fibrinogen is greatly diminished or absent.[9, 45]

Activation of this system could also explain the findings reported recently by Kellogg[20] in his summary of twenty-three cases of premature separation of the placenta. Only five patients in his series recovered. There was evidence of a hemorrhagic tendency in seven patients, and in three cases the blood was uncoagulable. One patient who died, although blood loss was slight, had evidence of very rapid fibrinolysis in her blood. One case of our own, although blood coagulation was not disturbed, had very active fibrinolysis. Could not premature separation of the placenta be due to an activation of a proteolytic system in the decidua? It could be compared with an attempt to menstruate in spite of the pregnancy. Since the enzyme cannot escape as with the menstrual flow, it invades the maternal system. The higher incidence of premature separation of the placenta in toxemia pregnancies may relate these two conditions.

Although a study of the fibrinolysin system was not made in the four cases treated with heparin, the response to heparin in these cases may indicate that the fibrinolysin was involved. The two severe cases of pre-eclampsia required large amounts of heparin to produce an anticoagulant effect, while the eclamptic patient had a marked response from a small dose of heparin. If a coagulant system alone were involved in the mechanism of toxemia, one would expect that with progression of the disease there would be increasing resistance to heparin and more would be required to produce an anticoagulant effect. If the fundamental mechanism were due to activation of the fibrinolysin system, there

would be first a coagulant and then finally an anticoagulant action which would require decreasing amounts of heparin to produce an anticoagulant action as the severity of the disease increased. The response to heparin in these cases fits the latter. That is, the eclamptic required much less heparin than the pre-eclamptic patient to produce an anticoagulant action. Such a response suggests that possibly the fibrinolysin system is activated in toxemia.

From the references and data presented one can formulate a possible mechanism to explain the activation of the coagulant and fibrinolysin systems in toxemia of pregnancy. It may be briefly outlined as follows: With catabolic changes in the cells of the endometrium, decidua, or placenta, enzymes may be released which can invade the general circulation. Catabolism may occur as a result of withdrawal of hormonal support or anoxemia which may occur during menstruation, in premature separation of the placenta, in toxemia of pregnancy or toward the end of a long labor. The activators released, such as thromboplastin, fibrinokinase, and possibly others, are normally neutralized by specific inhibitors. But if the inhibitors are inadequate, then the respective enzyme systems may be activated.

Such a situation may exist in toxemia of pregnancy. Thromboplastin initiates the conversion of prothrombin into thrombin and thus releases an active coagulant. Fibrinokinase activates profibrinolysin to form fibrinolysin which is first a coagulant and then an anticoagulant. It may destroy prothrombin, fibrinogen and fibrin. It may be cytotoxic. As a result of such changes, in toxemia of pregnancy, blood clotting may be at first more rapid and then more prolonged as prothrombin and fibrinogen are destroyed. Early there may be widespread thrombosis, and later there may be hemorrhage into various tissues. Terminally, the blood will not clot and fibrinogen is absent.

Such a hypothesis gives an explanation for Obata's results.[28] If the placental extract contained thromboplastin and fibrinokinase, injection of the extract into animals would activate the clotting and proteolytic systems and produce in sequence thrombosis, hemorrhage, and uncoagulable blood as Obata observed. Normal serum,[28] heparin,[36] and soybean trypsin inhibitor[13] protect the animals from the extract by neutralizing these enzymes. Pre-eclamptic and eclamptic sera are unable to neutralize the placental toxin, because the thromboplastin and fibrinolysin inhibitors are depleted in these patients.

It may be that menstrual toxin is an activator of the fibrinolysin system and that the protective pseudoglobulin is effective because of antifibrinolysin action. The coagulant and proteolytic enzymes found in the placenta by Hofbauer may be thromboplastin and fibrinolysin. Thus, to control more of the factors which are responsible for the blood changes in toxemia, it is likely that not only anticoagulant but also antifibrinolytic measures must be used.

Conclusions

1. Heparin is not effective in the therapy of toxemia of pregnancy.
2. Its failure is strong evidence against the thromboplastin theory of toxemia in pregnancy.
3. Its failure does not test the hypothesis that there is a disturbance in the fibrinolysin system in toxemia of pregnancy, and that this disturbance may be responsible for the reported changes in the clotting mechanism in toxemia.

It is a pleasure to acknowledge the great assistance in this work rendered by technician, Miss Sally Davis, and by the Sloane Hospital nursing staff.

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RELATIONSHIP OF THE ENDOMETRIUM TO THE CHORIOPLACENTAL DEVELOPMENT AND ITS GONADOTROPHIN OUTPUT*

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THE successful growth and development of the embryo depend upon many reciprocal physiological relationships. First, the ovum itself must be extruded from the Graafian follicle without "germ plasm defect" and must arrive in the cavity of the uterus in a normal state. Second, the endometrium must prepare a situs for implantation by proceeding to the true secretory state under the stimulation of estrogen and progesterone. Third, the trophoblast must develop a satisfactory chorion which can later establish a complete hemotrophe system for the growing embryo. Fourth, the cells of the chorion must secrete adequate amounts of chorionic gonadotrophin in order to maintain the corpus luteum and stimulate the secreting function of the decidua. This reciprocal hormonal and metabolic balance must go on at all times in order to insure proper nutrition for embryonic growth and a successful pregnancy.

The purpose of this presentation is to discuss the secretory qualities of the endometrium and its responsibility in developing a normal chorion and hormonal output. The endometrium has long been classified in the various phases of the cycle by the histological changes that occur at those times. These changes have occurred in the stroma, vascular systems, and endometrial glands. It has been designated, after ovulation, as the secretory phase. Although these microscopic changes have been a measure of activity of these endometrial structures, they have not completely evaluated their functions. I would like to emphasize that the endometrium should be considered as a highly specialized, secreting membrane putting out many materials for nutrition of the fertilized ovum, and that it should be further evaluated for these substances by histochemical and biochemical methods.

It is not known at present what the fertilized ovum has expected from the endometrium. It is a fact, however, that the blastocyst must obtain its nourishment from the secretion of the endometrium, particularly during the first weeks of intrauterine life. It is also during these early days of implantation that this fragile embryonic structure has need for a type of food well adapted for rapid growth. There are probably many materials that are put out by the endometrium which are necessary for the ovum.

We have examined the endometrium for carbohydrates because we have felt that these compounds must be basic substances for the growing blastocyst. It has been found that carbohydrates are present in the secretions of the endo-

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trium and that they are necessary for satisfactory ovulation and proper implantation. We have felt that the amount of carbohydrate present in the endometrium is a measure of its quality. Certain structures of the endometrium are responsible for the metabolism of sugar, and this process goes on in the same chemical manner as in other tissues of the body where glycogenesis takes place. These normal changes were noted by studying the endometrium in sixty-eight normal women. The endometrium was removed on various days of the cycle and was evaluated by noting the amount and location of glycogen, alkaline phosphatase, other glycogen-splitting enzymes, and vitamin C. It was found that these substances were present in characteristic amounts in the glands and arterioles of the endometrium at the time of implantation. These data have been previously published.[1] From these observations we have felt that the metabolism of sugar was an essential function of the endometrium and was probably only one of the many processes which go on in this tissue. Carbohydrates were also considered as a basic material for the nutritional requirement of the egg. These metabolic processes were under the influence of estrogen and particularly progesterone. However, the follicle-stimulating hormone and luteinizing hormone released by the anterior lobe of the pituitary were directly responsible for the ovarian output of hormones.

The prospects of ovular survival were good when the endometrium had ample amounts of available food. The trophoblast grew rapidly after implantation, becoming differentiated into the syncytiotrophoblast and cytotrophoblast. This chorionic development not only assured a system of obtaining nutrition for the embryo, but also secreted chorionic gonadotrophin in increasing amounts. This hormone through its luteotrophic effect on the corpus luteum caused further metabolism to go on in the newly formed decidua. The chorionic villi, when the endometrium was fully secretory, developed a good syncytiotrophoblast and well-preserved cytotrophoblast. These latter cells, further designated as Langhans' cells, produced the chorionic gonadotrophin. It has been a well-known fact that the level of this hormone increased to its maximum about the ninetieth day of gestation when it began to decrease in amount. The function of the cytotrophoblast began to wane from this time until about the one hundred and twentieth day of gestation when these cells had almost disappeared.

This reciprocal relationship may be altered by many factors and as a result faulty formation of the chorion may occur. Failure of the trophoblast to develop in the normal manner may be the result of several intrinsic factors. These may be defects in the germ plasm as demonstrated by Hertig[2] in his studies of early ova. The endometrium or the maternal environment may be deficient in nutritive materials. Mall and others have reported environmental alterations as the cause of imperfect ovular growth and abortion. These two anatomical defects probably go together as combined factors in connection with poor placentation, ovular death, or malformation.

Material

We have attempted to correlate these facts in a study of the endometrium of 324 patients who had given the history of sterility, abortion, or both. All

patients were completely studied. There was a total of 996 endometrial observations completed in this group. Samples of the endometrium were reviewed on the 26th day of the cycle. The specimens were studied for carbohydrate metabolism and enzyme production. We found that 58 per cent of these patients did not have normal glycogenesis in the endometrium. In 15 per cent of this group the endometrium remained in the proliferative phase without glycogen, but with ample amounts of alkaline phosphatase. When this picture was observed, sterility was generally the chief complaint. In the other 85 per cent there were minor and major changes found in the endometrium. In some the endometrium was scanty in glycogen, even though histologically the picture of a secretory endometrium was noted. In a smaller group the amount of alkaline phosphatase was diminished in amount and there was a poor vascular development. In other words, there was no definite correlation between glycogen output and phosphatase reaction. In 77 patients the production of the glycogen-splitting enzyme was lower than normal, averaging 16.6 mg. per gram of tissue. The normal amount of this enzyme was 36.9 mg. per gram of tissue. The amount of vitamin C was also below normal. The endometrium had preceded to a secretory type of tissue histologically but had failed functionally to produce these materials. Table I illustrates these percentages.

There was a total of 126 abortuses that were studied in an attempt further to correlate the type of endometrium and pathological findings of the abortus. On close examination of these specimens, the following pathological diagnoses were given by the pathologist:

1. Thrombosis, necrosis, and hemorrhage occurred in 30.9 per cent.
2. Immature development of the chorionic villi was noted in 59.9 per cent. The notable features in this group were avascularity, edema, and failure of the development of Langhans' cells. The embryo had died early in pregnancy, although this condition existed in some even though the embryo was expelled alive.
3. Premature separation of the circumvallate formation of the placenta was found in 5.3 per cent. This occurred in cases in which abortion occurred later in pregnancy.
4. Degeneration of the products was given as the diagnosis in 3.9 per cent. It was also important to note that in many cases there was an overlapping of this condition. The endometrium was noted to be of poor quality in 71 per cent of these cases.

The output of chorionic gonadotrophin was affected by these unusual pathological changes which occurred in the villi. Chorionic gonadotrophin titers in 40 patients were done previous to abortion. These levels did not increase to their normal amounts when the cytotrophoblast failed to develop. In some, the layers of the trophoblast were fairly well preserved, but there was edema of the stroma noted together with avascularity. The level of chorionic gonadotrophin in these individuals was somewhat higher, although it did not reach the normal level. It would seem from these estimations that it may be possible to predict the condition of the abortus. However, other tests must be done and many cases must be accumulated before definite statements can be made concerning this fact. It is important to evaluate the output of progesterone because it has been noted that when the chorionic gonadotrophin output was low but the secretion of progesterone was normal or even higher than normal the pregnancy continued. This situation was observed in a few patients. However, certain complications occurred later. These were premature labor, abruptio placentae, and immature development of the fetus itself. The pathological changes noticed in the placenta of these patients were similar to those recorded in the early abortuses, namely, immaturity, avascularity, and edema of the villi.

TABLE I. PERCENTAGE OF ENDOMETRIAL CHANGES

PROBLEM	SPECIMENS STUDIED	NO.	PERCENTAGE
Sterility	176	77	43
One previous abortion	42	23	54
Two previous abortions	54	48	83
Three or more abortions	52	48	86

Examples of endometrial, chorionic, and hormonal relationships will be cited in the following three cases:

CASE 1.—The first pregnancy of Mrs. M., aged 32 years, ended in the sixth month with spontaneous, premature labor of twins. Placenta showed some immature villi. There was some difficulty in becoming pregnant again. The endometrium was studied and was found to be in a poor secretory state (Fig. 1). Pregnancy did occur, however, without treatment. Spontaneous abortion occurred at the end of the second month.

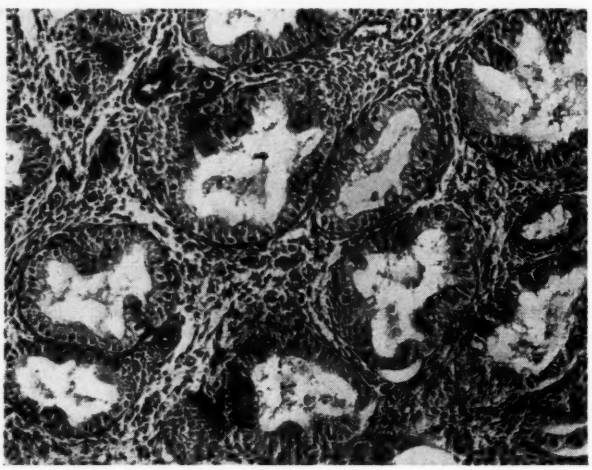

Fig. 1.—This endometrium was removed on the 26th day of the cycle when glycogen and alkaline phosphatase should be found in large quantities in the glandular lumen and the endothelium of the spiral arterioles. This endometrium taken from Case 1 shows diminished quantities of alkaline phosphatase, a few poorly formed arterioles, although histologically it is typical of a secretory phase.

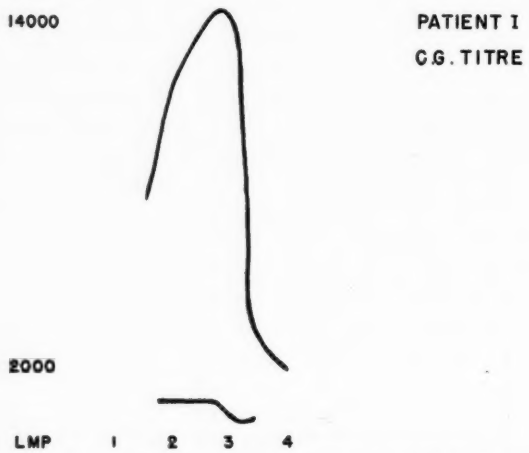

Fig. 2.—Upper curve is typical of chorionic gonadotrophin output in the normal patient. Lower curve demonstrates the amount of chorionic gonadotrophin in Case 1.

Pathological diagnosis of the abortus: immaturity of the villi.

The third pregnancy proceeded normally until the second month when bleeding and cramps began to occur. Chorionic gonadotrophin titers failed to rise over 1,000 hyperemia units on six different occasions (Fig. 2).

Pathological report of the abortus was abnormal villi and necrosis of the decidua (Fig. 3). The endometrium still remained in a poor secretory condition.

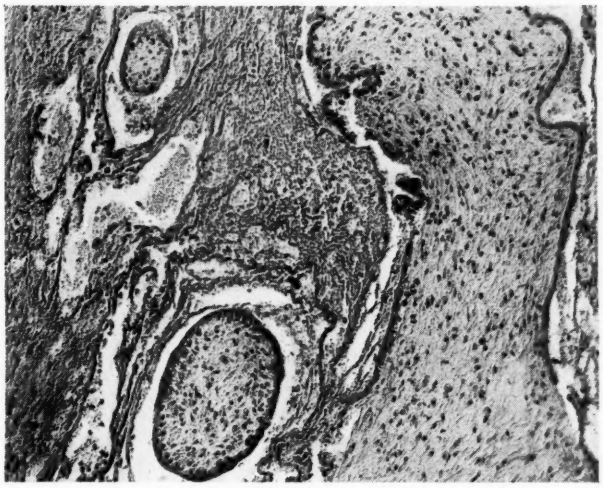

Fig. 3.—Necrotic decidua. Villi without normal architecture. Failure of development or degeneration of cytotrophoblast cells. (× 140.)

CASE 2.—Mrs. R., aged 29 years, had a history of sterility. Her first pregnancy ended in a severe pre-eclamptic toxemia. The fetus survived. The patient remained in good health. A period of sterility of three years was next noted. The sterility was based upon the irregularity in ovulation as shown by endometrial biopsies and poor temperature curves.

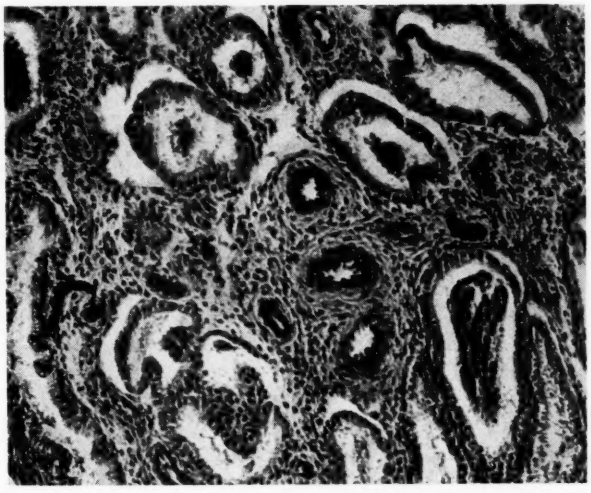

Fig. 4.—Twenty-sixth day endometrium. Practically no alkaline phosphatase in the glands. Fair glandular development. Poor arteriolar formation. Some vessels have alkaline phosphatase. Glycogen, although not shown in this section, was scanty in amount. (× 140.)

Pregnancy occurred after treatment. At the end of three months' gestation, bleeding began which lasted for six weeks. The chorionic gonadotrophin titer failed to increase over 3,000 hyperemia units. Spontaneous abortion occurred and the placenta showed immature de-

velopment of the villi. The fetus was small and underdeveloped. The patient again attempted pregnancy one year later. This pregnancy ended at the third month. There was bleeding for one month prior to the abortion, during which time the chorionic gonadotrophin titer increased to 4,000 hyperemia units. The placenta again showed immature development of villi. Repeated endometrial biopsy showed a diminution of glycogen and phosphatase output. The type of endometrium found is illustrated in Fig. 4. The levels of chorion gonadotrophin are shown in Fig. 5, and the pathological development of the second abortus is shown in Fig. 6.

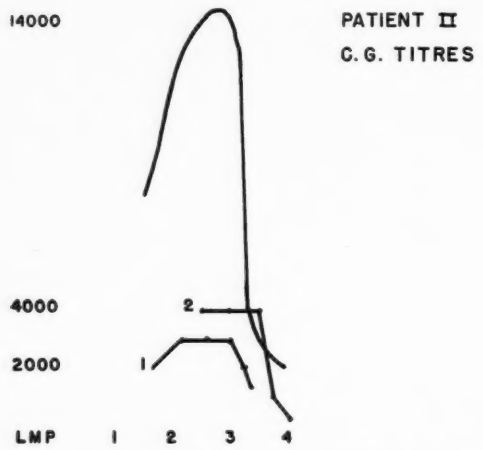

Fig. 5.—Upper curve is the average normal chorionic gonadotrophin output. Curve 1 shows the output of chorion gonadotrophin during the first abortion. Curve 2 shows the output of chorion gonadotrophin during the second abortion.

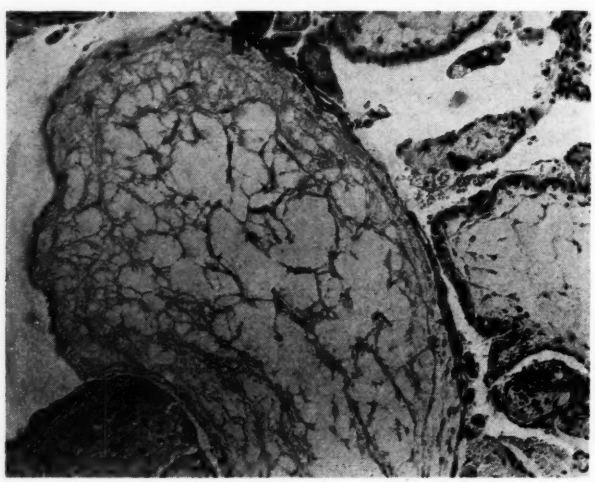

Fig. 6.—Large edematous villus. Other immature villi. Decidua in lower left corner. Avascularity of villi noted. (× 140.)

CASE 3.—Mrs. P., aged 35 years had a history of an eight-year sterility and one previous miscarriage. The cause of sterility was found to be irregular ovulation as shown in the endometrial biopsies. The endometrium was abnormal as shown in Fig. 7. The patient was treated. The endometrium improved somewhat but did not become full blown in character. Pregnancy occurred after this treatment. Six weeks after conception the chorionic gonadotrophin titer failed to increase over 6,000 hyperemia units (Fig. 8). Bleeding began, and the patient aborted spontaneously.

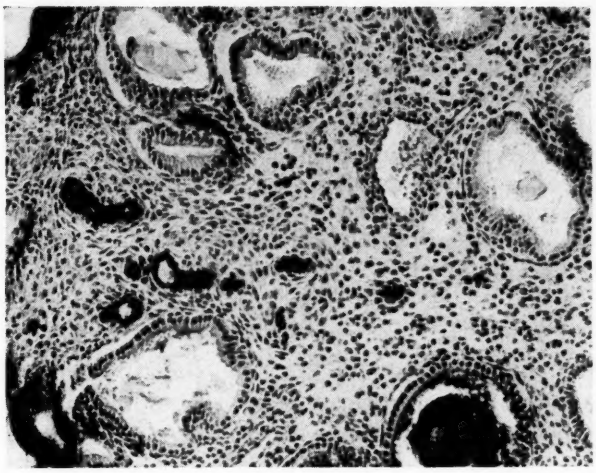

Fig. 7.—Twenty-sixth day endometrium, secretory. Most glands failed to show alkaline phosphatase. Glycogen was diminished in amount. Some vessels noted with alkaline phosphatase. Some vessel distention. (× 140.)

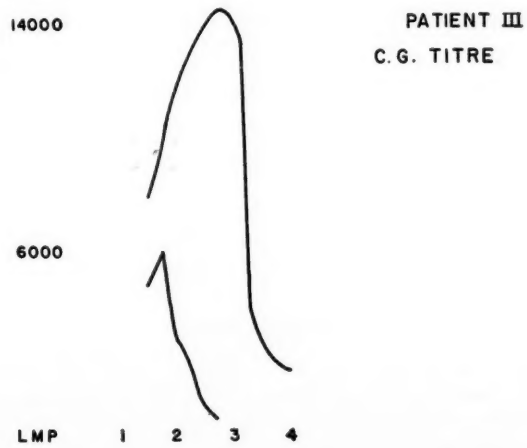

Fig. 8.—The upper curve is the normal chorionic gonadotrophin output. The lower curve demonstrates the chorionic gonadotrophin output in Case 3.

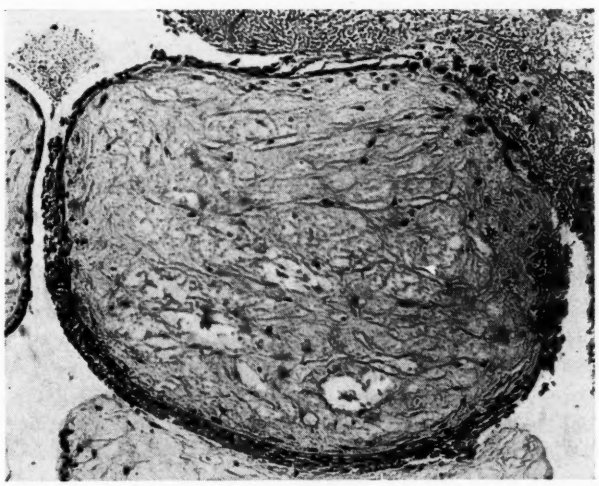

Fig. 9.—Abortus. Marked edema with avascularity of villi. Langhans' layer practically nonexistant. (× 140.)

Pathological diagnosis of the placenta was immature development of the villi (Fig. 9). The endometrium remained in a poor secretory state.

There have been many other cases that have shown these trends: poor endometrium, poor chorion, and failure of the cytotrophoblast to produce chorionic gonadotrophin. The satisfactory treatment of these patients should be directed to the improvement of the condition of the endometrium prior to conception. The possibility of producing a normal chorion becomes remote when fertilization takes place in a poor environment.

Conclusions

1. The development of the trophoblast depends upon a normal germ plasm, adequate secretion from the endometrium, and enough chorionic gonadotrophin to stimulate the decidua to put forth adequate amounts of food for growth of the embryo.

2. If any one of the relationships is altered, the possibilities of good chorion development are reduced.

3. Complications in early pregnancy, such as abortion, result from this alteration.

4. The endometrium is the important tissue in this process supported by endocrine action.

5. Faulty endometrium is associated generally with endocrine abnormalities.

6. The endometrium must be improved by endocrine therapy before gestation. This must be done if a successful pregnancy is to be expected.

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Discussion

DR. J. THORNTON WALLACE.—For a number of years it has been recognized that there are many factors which may be responsible for infertility and abortion. Any one of these may be the causative factor in some cases, whereas in others a combination of two or more factors may be acting together. It is interesting to look back on their evolution, particularly those related to the female sex hormones and the vitamins. Through its isolation from the corpus luteum by Allen and Corner, progestin was one of the first hormones to be made commercially available. It was hailed with considerable enthusiasm as possibly the solution to the problem of threatened abortion, and of habitual abortion as well. About

this same time Shute and his associates brought out their ideas of the relationship of vitamin E to infertility and abortion. Both these substances, however, failed to produce the hoped-for clinical results.

The synthesis of estrogenic hormone then established it as the most potent female sex hormone available for oral administration. Some five or six years ago Dr. Norris Vaux read a paper before this society giving his results with the use of a combination of the estrogenic and progestin hormones in habitual abortion. His results have not been widely confirmed.

The form of hormonal therapy which enjoys the greatest popularity at present is that advocated by Smith and Smith, Karnaky, and others. Small doses of the estrogens are given in both infertility and habitual abortion to improve the endometrial bed for the reception of the fertilized ovum and very large doses after conception to maintain the pregnancy. Javert has more recently emphasized the role of vitamin C in these situations. None of these agents has proven efficacious in all cases. It is probable, as Dr. Hughes has indicated, that it is a properly coordinated reciprocal relationship between these and possibly other as yet unknown factors which will produce the solution to this most baffling problem. Dr. Hughes' investigations contribute another factor, that of the glucose content of endometrial tissue. It may well be that whatever good results are to be obtained from hormonal therapy may be through the stimulation of the endometrium to retain and store greater quantities of glucose which will in turn serve to nourish the early embryo better. There has recently been a revival of interest in the relation of progestin to abortion and as more potent preparations become available it may yet be possible, through their powerful influence on the endometrium, to sustain pregnancy in threatened and habitual abortion by improving chorionic development. It would seem from Dr. Hughes' investigations that the need for vigorous supplementary progestin therapy may be predicated on excretion levels of chorionic gonadotrophin.

It would be interesting to know just what percentage of the 75 patients whose abortuses showed immature development of the chorionic villi likewise showed lowered glycogen content in their endometrium in the nonpregnant state.

The exact role of the glycolytic enzymes, alkaline phosphatase, and vitamin C is not yet clearly defined. However, with the amount of attention that is currently being focused upon these substances, the answer may ultimately emerge.

DR. J. EDWARD HALL.—Some of this work has at least been corroborated in this city. Members of this Society will recall a paper read before them on the role of alkaline phosphatase in the endometrium where it was shown that our findings were exactly the same as those of Dr. Hughes.

We went a little further in determining the alkaline phosphatase by histochemical means in the chorionic epithelium and the decidua and found that in the decidua there was an absence of this substance, whereas in the chorionic epithelium it was present in considerable amount. We are not certain, at the present time, of the significance of these findings. I would like to ask Dr. Hughes if he found any similar situation and, if so, what his interpretations are.

I also would like to ask him about the relationship of some of these placentas and villi which he described as immature. I wonder if some of them are not due to degenerative factors that have taken place after the death of the ovum. It is sometimes very difficult to determine whether the placenta itself was immature in development, or whether a degenerative process had set in.

DR. SAMUEL A. WOLFE.—A functionally adequate decidua is a prime requisite for the implantation and growth of the previllous ovum. This in turn depends upon the corpus luteum. In early pregnancy this structure is enlarged. Its epithelial column is wide and markedly convoluted and the bright yellow color lends gross evidence of the high lipoid content so indicative of heightened functional activity. Pregnanediol determinations of the urine prove this concept. A deficiency in the corpus luteum may be present from the time of its inception and so results in a defective decidua. On the other hand, this may mirror only the primary inadequacy of embryonic trophoblast for chorionic gonadotrophin

stimulates the pituitary to maintain adequate lutein and luteotrophic hormone. The enigma therefore still remains whether the blighted ovum and the miscarriage resulted from a poor "germ plasm" or a poorly developed decidua. Similiarly, the immature villi shown in this series may well be interpreted as "hydropic villi" with edema and degeneration of the mesenchymal stroma after death of the ovum.

In habitual aborters studied between pregnancies several endometrial biopsies may well reveal inadequacies in the endometrium by alkaline-phosphatase and glycogen stains, yet serial study over many months will reveal that this is not constant. It cannot, therefore, be inferred that the decidua associated with the current pregnancy was primarily deficient or functionally inadequate. Tissues, both fetal and maternal, are hardly adequate for deductions as to function after death of the embryo has occurred.

DR. STANLEY C. HALL.—What is the practical application of this study?

DR. MORRIS GLASS.—Has Dr. Hughes attempted to correlate the estrogenic and the pregnandiol secretion with some of these specimens of endometrium? He made a diagnosis of defective endometrium in the absence of ovulation. It seems to me that the effect of such a study is important in interpreting some of these cardinal changes in the endometrium.

It would probably be of interest to describe degeneration of the villi as an increase of the endometrium, in women who have been bleeding, because so frequently bleeding continues for some time before the products of conception are extruded. This is a common finding.

I have been impressed with the use of large doses of progesterone in the treatment of threatened abortion. A great many of these patients cease to bleed and the bleeding is replaced by a "dirty brown" discharge following which, after a period of time, the products of conception are extruded. There is a distinct time element in the process. I wonder if Dr. Hughes has taken into consideration this time element from the actual onset of bleeding and the final diagnosis of immature villi.

DR. FRANK P. LIGHT.—For a number of years, many clinicans have felt that treatment of threatened abortion was useless since most of the abortions were thought to be due to defective ova. However, many patients with threatened abortion were successfully carried to term and delivered normal infants.

We now hear that Dr. Hughes believes that defective endometrium is frequently the cause of the loss of an early pregnancy. I trust that this idea will not be overemphasized.

DR. HUGHES (Closing).—Dr. Wallace has discussed the various methods of endocrine therapy. We have all tried estrogen, progesterone, together with the combination of both, but there is still a good percentage of failures. We have felt that there is about a 30 to 35 per cent salvage rate. It depends upon a good decidua with a good formation of the chorion and also upon a good ovum. We believe that attempts should be made to improve the endometrium before pregnancy takes place. This is particularly true in cases classified as habitual abortion. We have found that small doses of diethylstilbestrol (0.1 mg.) or Premarin (0.3 mg.) during the preovulatory phase gave the best results. Larger doses of diethylstilbestrol (0.5 mg.) tended to inhibit ovulation.

Dr. E. Hall has asked about the changes in the decidua and chorionic villi. We have noted, rather consistently, early thrombosis, hemorrhage, and almost sterile necrosis in the decidua. Associated with these findings the villi were immature in nature. These changes were so consistently found even when the embryo had been aborted alive or had recently died that there seemed to be a rather definite correlation. We have noted that phosphatase was present in the decidua where glycogen was located, but it was not evident on the fetal side. We have not examined enough, however, to stress this point.

Dr. Wolfe has remarked about the influence of the corpus luteum. There is no question that it is the essential structure needed for the stimulation of the decidua at least until the placenta has developed. Does the pituitary continue to stimulate the corpus luteum

after conception so that progesterone can be produced, or does the chorionic gonadotrophin from the chorion carry on this function? We do know that chorionic gonadotrophin is luteotrophic and when given during the early part of pregnancy will increase the pregnandiol output. We have tried chorionic gonadotrophin in various dosage. Small amounts seem to improve the pregnanediol output and increase the levels of chorion gonadotrophin while large doses have depressed these outputs.

Dr. Wolfe has also discussed the variations of the cycle which may occur at times. We have made many observations particularly by endometrial biopsies which bear out this point. These examinations show that the endometrium may be better at various times of the year even though there has been no treatment. However, if conception should occur when the endometrium is of poor quality, poor implantation may result. When the endometrium remains consistently poor, there is even greater opportunity for abortion.

Dr. S. Hall has asked, "What are the practical applications of this study?" There are some women who have a poor endometrium and are more prone to abortion. This is particularly true in those individuals known as habitual aborters. Although some feel that one must have at least three abortions to be considered in this category, we feel that after one there is a greater opportunity for repeated abortions. This is particularly true if the pathological findings which were described tonight are found in the abortus.

We have found that there is a better opportunity for ovular salvage when the endometrium was normal or was prepared before conception as described earlier. If the endometrium was poor to begin with or was not improved by treatment and there was poor chorion formation, the hormonal levels were low and the results were not good, irrespective of the treatment employed.

Dr. Glass has asked about estrogen. We have noted that both estrogen and progesterone are essential for the entire process. We have felt that the action of these hormones upon the endometrium was different. The former in small doses affected the vascular system while the latter caused the glands to become more active. The blood supply seemed to be the important factor. We have all used these hormones without satisfactory results. It depends upon the dosage and response of the pituitary, ovary, and endometrium to these hormones. If the pregnanediol and chorionic gonadotrophin levels do not increase after conception or after any type of therapy, there is no sense of continuing with the treatment. By routine determination of these hormones we have ruled out the patients that should not be treated. There was one group of four patients in whom the chorionic gonadotrophin titer remained low after treatment who went to term. In all cases various accidents occurred in the latter part of the pregnancy. In some of these, examinations of the placenta showed pathological changes similar to those found in abortuses.

In conclusion it seems quite essential that we have good implications, good chorion, and good hormonal relationship if the pregnancy is to continue to term successfully.

AN APPRAISAL OF CHORIONEPITHELIOMA BASED ON OBSERVATIONS IN TWELVE CASES*

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THE diseases affecting the chorion are among the most intriguing problems in gynecology. Hydatidiform mole is seldom seen and chorionepithelioma is rare in the personal experience of any one man; the bizarre picture of these diseases, their biological and pathologic vagaries, make them extremely interesting. The authors' attention was focused on this problem by their observations of twelve cases of chorionepithelioma.

On review of these cases, one is impressed by the rapidly fatal course in the majority. We wish to appraise in this presentation all the known facts concerning these cases, with special reference to methods of diagnosis, evaluation of the biological tests, classification of growth, treatment and results.

The observations and comprehensive reviews of literature published by Marchand,[1] Ewing,[2] Essen-Möller,[3] Frank and Geist,[4] Mathieu,[5] Teacher,[6] and Novak[7] greatly facilitate the study of this subject and render unnecessary a review of the classification and pathologic features of this disease, as well as any complete bibliography.

Case Reports

CASE 1.—G. F., aged 24 years, gravida i, was curetted for an incomplete abortion Feb. 10, 1947. Pathologic description: Portions of spongy tissue with vesicles arranged in grapelike clusters. The chorionic villi were greatly enlarged, with edematous and acellular stroma, and lined by Langhans' and syncytial cells showing moderate proliferation. No malignant changes were noted. Diagnosis: *Hydatidiform mole.* Vaginal bleeding recurred, and two subsequent Aschheim-Zondek tests were negative. On June 2, A-Z test was positive. Vaginal examination showed uterus to be boggy and enlarged to the size of a two-month gestation. A large amount of fleshy mole tissue was removed at this second curettage. Sections (Fig. 1) showed islands of decidua with trophoblastic elements which consisted of compact polyhedral cells aligned in mosaic-like arrangement. The nuclei were vesicular, irregular, and showed well-stained nucleoli. Adjacent to these islets were seen syncytial cytoplasmic masses containing many nuclei which were bizarre-shaped and hyperchromatic. Occasional mitotic figures were seen among them. The above elements represented Langhans' as well as syncytial components, the former predominating. Diagnosis: *Malignant choriomatous transformation of a hydatidiform mole.* X-ray of chest revealed numerous metastatic foci throughout both lungs. A supracervical hysterectomy was performed. Gross examination of excised uterus showed a reddish, ragged, fleshy tumor mass, 2 by 2 by 1 cm., just above the internal os, which extended from the endometrium through the entire myometrium. Microscopically, sections from the hemorrhagic area showed large masses of compact polyhedral Langhans' cells, the nuclei of which were vesicular, irregular in size and shape, and contained a goodly number

*Presented at a meeting of the Brooklyn Gynecological Society, Nov. 16, 1949.

of mitotic figures. There were also many masses of syncytial cells with bizarre-shaped, hyperchromatic nuclei. The histologic appearance was practically identical to that seen in second curettings. Diagnosis: *Chorionepithelioma of the uterus.* Patient was subsequently irradiated and the pulmonary foci disappeared radiologically. On September 5 the patient had an attack of hematuria which required ligation of two vesicular arteries. Examination revealed vaginal, pulmonary, and parametrial metastases. On September 19, a left-sided hemiplegia developed and the patient became comatose and expired. No autopsy. *Final diagnosis: Chorionepithelioma of the uterus with metastases to lungs, bladder, vagina, and brain.*

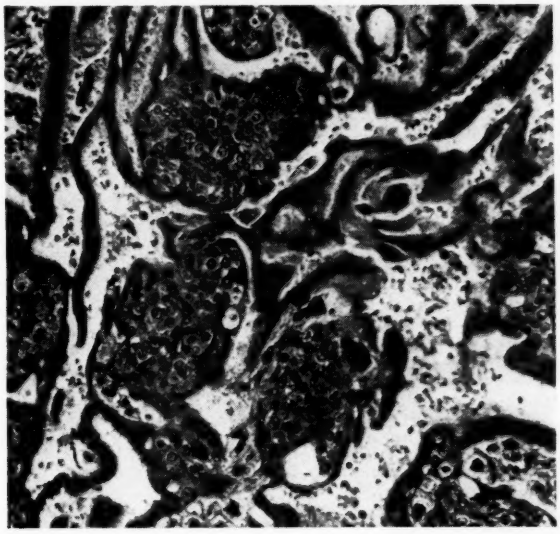

Fig. 1.—Case 1. Uterine curettings.* The Langhans' cells greatly predominate and are arranged in compact masses. Mitoses are numerous. Note also the ribbonlike bands of syncytium. (×220.) Diagnosis: Chorionepithelioma.

CASE 2.—A. W., aged 19 years, gravida i, was curetted for an incomplete abortion on Jan. 3, 1947. Vesicles were observed on gross examination. Pathologic diagnosis: *Placental tissue with hemorrhage and necrosis.* Subsequently patient complained of intermittent vaginal bleeding from March 3 to June 18. Hemoptysis occurred April 15. The uterus was enlarged to the size of a twelve-week gestation. The A-Z test was positive. Lungs were clear. A curettage revealed a large amount of pinkish grumous material. Microscopically, there were many large masses of both Langhans' and syncytial cells. The former showed the nuclei to be irregular, with numerous mitotic figures. The syncytial cells showed the nuclei to be hyperchromatic and bizarre-shaped. In addition, large islands of endometrium with a decidual stroma were present. Pathologic diagnosis: *Choriocarcinoma of the uterus.* On Jue 27 a total hysterectomy and bilateral salpingo-oophorectomy were performed. Grossly, at the level of the internal os, the uterus revealed an area of excavation, with a ragged, reddish polypoid tumor mass above it. The latter projected into the uterine cavity and invaded the myometrium. Microscopically, the tumor mass revealed a picture similar to the one previously described. The pathologic diagnosis was: *choriocarcinoma of the uterus and cervix.* On July 7 patient suddenly developed a right-sided hemiparesis, became comatose and expired. Spinal fluid showed "cancer cells." Autopsy not performed. *Final diagnosis: Choriocarcinoma of uterus and cervix with metastases to lungs and brain.* On subsequent review of the first curettings evidence of malignancy was found (Fig. 2).

*Due to limitation of space, many gross pictures and photomicrographs could not be published. All of the figures herein have been chosen in an effort to present of each case a representative section of the lesion. It is important to point out that the presentation of a general histologic pattern by a single photomicrograph must necessarily be incomplete.

CASE 3.—F. F., aged 23 years, gravida ii, had a 14-week miscarriage and was curetted on April 10, 1947. Grossly, vesicles were observed. Microscopically: the villi were greatly enlarged with edematous avascular cores and a moderate amount of trophoblastic proliferation.

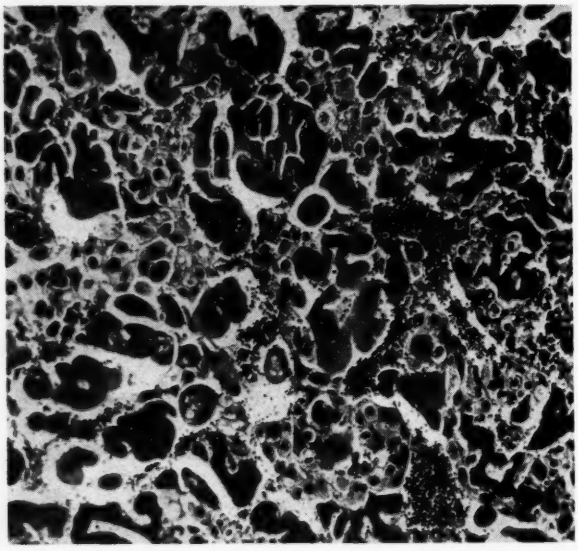

Fig. 2.—Case 2. Uterine curettings. The syncytial cells are arranged as multinucleated pseudogiant cells or in anastomosing columns. The Langhans' cells, characterized by their distinct cell borders, are arranged in solid sheets. Both variety of cells show marked anaplasia. Mitoses are found in moderate numbers. (×120.) Diagnosis: Chorionepithelioma.

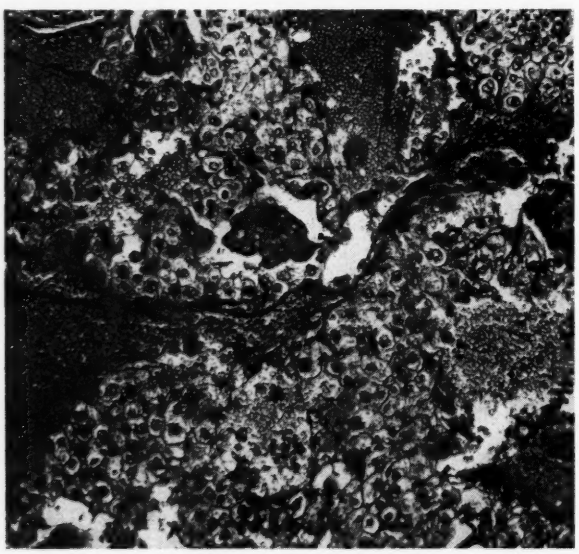

Fig. 3.—Case 3. The normal lung parenchyma has been replaced by a tumor mass, amidst which areas of hemorrhage and necrosis abound. The tumor is composed mainly of well-defined, polyhedral Langhans' cells arranged in solid sheets. A multinucleated syncytioplasmic mass is seen in the center of the figure. (×110.) Diagnosis: Chorionepithelioma of the lung.

There was, however, one small area where the Langhans' cells were slightly atypical. Diagnosis: *Hydatidiform mole.* A-Z test, October, 1947, was negative. (All the above information was obtained after patient expired, when the case presented itself as a diagnostic problem.) Her menstrual periods were regular up to Feb. 15, 1949, when intermittent vaginal

bleeding began, and because of the latter and a history of infertility a hysterogram and a curettage were performed. They revealed a normal-sized uterus, with a submucous polypoid growth. Microscopic diagnosis of curettings was *endometrial hyperplasia.* Following curettage her bleeding had again occurred. On August 15 patient had several teeth extracted and bled profusely. She then noticed persistent hemoptysis. On September 2, x-ray showed a mass in the right lung and a normal left lung. On September 7 there was a marked increase in the size in the mass on the right, as well as numerous other nodules in both lungs. The uterus was found to be enlarged. Intravenous pyelogram, x-rays of long bones, spine, skull, and pelvis were negative. A small hemorrhagic mass in the occipital region was noted. Vaginal smears were negative for malignancy. On September 14 an A-Z test in 1:50 and 1:500 dilutions was positive. A provisional diagnosis of "chorionepithelioma of the uterus with pulmonary metastases" was made. On September 17 a total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was normal in size and shape and the endometrial cavity was smooth and regular. Microscopically, serial sections of the uterus revealed only decidual tissue without evidence of trophoblastic or tumor tissue. The ovaries contained several corpora lutea. Postoperatively the pulmonary masses progressively increased in size. A-Z test remained strongly positive. The patient became progressively worse, and expired on Sept. 21, 1949. The right lung revealed numerous friable dark-red nodules, scattered throughout the lung. Microscopically (Fig. 3) tumor areas showed replacement of lung parenchyma by compact masses of blood with islands of syncytial and Langhans' cells interspersed, showing all the typical histologic characteristics of malignancy. *Final diagnosis: Chorionepithelioma of the lung.*

Comment.—Although typical choriocarcinoma was present in both lungs, the uterus, on careful study, showed no evidence of chorionepithelioma and the curettings removed two and one-half years previously showed a simple mole with only one small area of atypical changes.

Case 4.—A. B., aged 33 years, gravida iii, was admitted Nov. 10, 1947, with severe pain in left chest of ten days' duration and a history of amenorrhea from August 15 to October 28, followed by intermittent vaginal bleeding. On admission, the left lung revealed a pleural effusion, the right, a round shadow. One week later x-ray showed an increasing amount of fluid in the left chest, and the mass on the right side had become much larger. Repeated thoracenteses were performed and 1,000 c.c. of a bloody fluid were obtained each time, which histologically showed a few "suggestive tumor cells." Pelvic examination was completely negative. On December 3 the A-Z test was strongly positive. Vaginal smears were negative for malignancy. Curettings showed no evidence of pregnancy or malignancy. An intravenous pyelogram, x-rays of the long bones, pelvis, spine, and skull revealed no abnormalities. The A-Z test was repeated and was strongly positive. A provisional diagnosis of "chorionepithelioma of both lungs" was made. Patient had a rapidly downhill course, and expired on Jan. 15, 1948. No autopsy. *Final diagnosis: Chorionepithelioma of lungs.*

Comment.—Although no definite histopathologic evidence is available, the history of three months of amenorrhea followed by irregular vaginal bleeding, with rapidly growing pulmonary masses, accompanied by persistently strongly positive A-Z tests make the diagnosis of chorionepithelioma a certainty.

Case 5.—B. C., aged 38 years, gravida v, had vaginal bleeding for one month, and gave a history of passing a hemorrhagic tissue. The microscopic diagnosis of "hydatidiform mole" was made. Six months later, patient had a severe vaginal hemorrhage, and hemoptysis. The uterus was the size of a three-month pregnancy. The lungs were studded with many round nodules of the cannon-ball type. The A-Z test was positive. A curettage was performed. The curettings showed numerous masses of syncytial and Langhans' cells (Fig. 4). The latter showed pleomorphism and hyperchromatism of the nuclei and many mitotic figures. The syncytial cells were arranged in typical creeping anastomosing cords and their nuclei were irregular and hyperchromatic with only rare mitoses. Diagnosis: *Chorionepithelioma of the uterus.* Abdominal operation was refused. Three weeks later patient had a profuse hemoptysis and expired. *Final diagnosis: Chorionepithelioma of uterus with pulmonary metastases.*

Comment.—It is noteworthy that here, as in other cases, it is mainly the Langhans' cells which exhibited mitotic activity. It is also interesting to note that islands of decidual tissue were present in the uninvolved area of the endometrium, a finding which was constant in almost all the cases presented here.

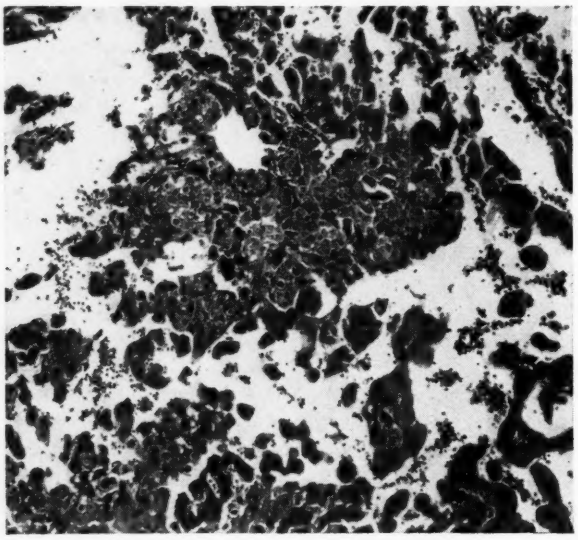

Fig. 4.—Case 5. Uterine curettings. The Langhans' and syncytial cells are closely intermingled. Note the budding, anastomosing character of the syncytium and the pleomorphism of the Langhans' cells. A number of mitotic figures can be seen by means of hand lens. (×110.) Diagnosis: Chorionepithelioma.

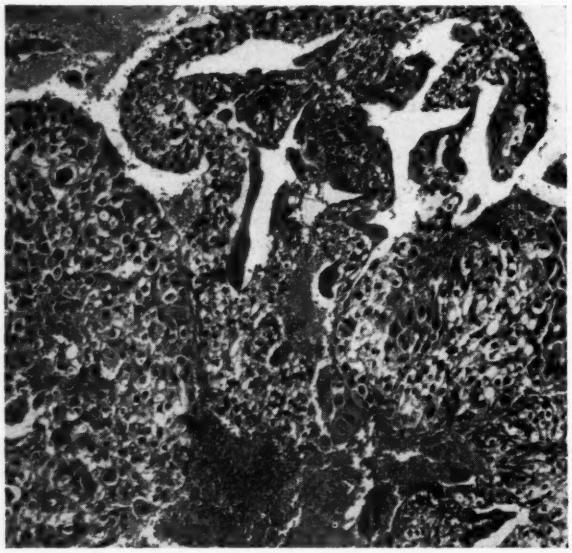

Fig. 5.—Case 6. First uterine curettings. The nuclei of the well-demarcated Langhans' cells show marked variation in size, shape, and tinctorial intensity, and a moderate number of mitoses. Multinucleated syncytial masses are noted. (×110.) Diagnosis: Chorionepithelioma.

CASE 6.—L. S., aged 45 years, gravida x, in fourth month of pregnancy, was admitted in cardiac failure, which was thought to be due to acute rheumatic fever. A mild toxemia, vaginal bleeding, and abdominal pain were also present. Her previous pregnancies had all been normal. On Nov. 9, 1948, vaginal bleeding became severe, and a curettage was performed.

Microscopically (Fig. 5) the villi were greatly enlarged, their cores edematous and avascular. Very considerable proliferation of the trophoblastic tissue was noted. The nuclei of the Langhans' cells showed variations in size, shape, and tinctorial properties. Mitoses were present in moderate number. Patient continued to bleed vaginally; A-Z test December 1 was positive. Subsequent A-Z test on December 10 was negative in dilutions of 1:25 and 1:50. One week later, a curettage of the uterus and biopsy of hemorrhagic mass in the vagina revealed "chorionepithelioma." On December 20 a total hysterectomy and bilateral salpingo-oophorectomy was performed. Ten days following operation, x-ray revealed evidence of metastases in both lungs. A-Z tests on Jan. 7, 1949, and January 19 were positive. Patient expired April 20, from bilateral bronchopneumonia superimposed upon metastases. No autopsy. *Final diagnosis: Chorionepithelioma of uterus with metastases to lungs.*

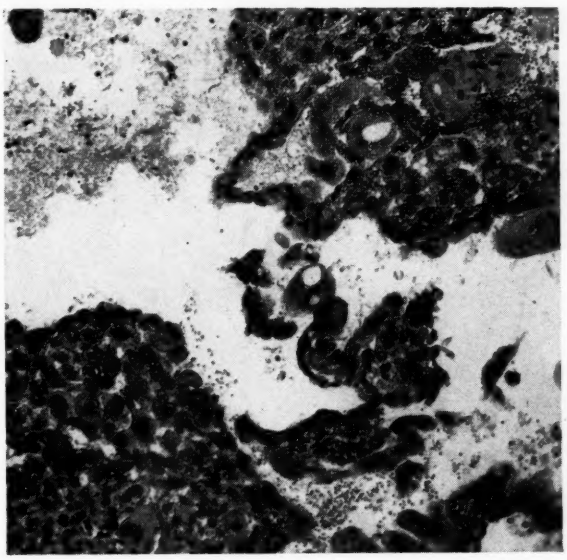

Fig. 6.—Case 7. The nuclei of the Langhans' cells show all the histologic characteristics of malignancy. The syncytial budding is clearly demonstrated. Slides of the metastatic nodule of the cervix show a similar picture. (×110.) Diagnosis: Chorionepithelioma of the uterus.

CASE 7.—B. S., aged 45 years, gravida iii, had intermittent vaginal bleeding since April 12, 1948, and had a supracervical hysterectomy with removal of left adnexa on June 4. The uterus was boggy and the endometrial cavity was filled with a large friable papillary mass exhibiting grapelike vesicles. Microscopically (Fig. 6) the chorionic villi were markedly enlarged in size. Many of the villi showed marked proliferation of the Langhans' and syncytical layers. The Langhans' cells showed pleomorphism and a goodly number of mitoses. The histologic picture was thus typical of a chorionepithelioma with a mole in situ. Patient continued to bleed vaginally. The cervix was removed on July 7. On gross examination it showed an ovoid excavation measuring 1.5 cm. in diameter, which contained a reddish friable tissue. Microscopically, amidst areas of necrosis and hemorrhage were seen islands of large, polyhedral Langhans' cells with dark hyperchromatic nuclei varying in shape, as well as scattered foci of syncytial cells. Mitoses were abundant. A diagnosis of "chorionepithelioma of the cervix" was made. Induration was felt in both broad ligament bases. Intensive irradiation was given to the pelvic region. A-Z tests on September 7 were positive, on October 27 negative, on January 12 and May 27, 1949, negative. X-rays on September 10 and June 8, 1949, were negative for pulmonary metastases. The patient was last seen on July 9, 1949, at which time there was no discernible evidence of residual or recurrent diseases. *Final diagnosis: Chorionepithelioma of uterus and cervix.*

CASE 8.—R. S., aged 34 years, gravida iii, was curetted for an incomplete abortion on July 12, 1945. Grossly, no distinct vesicles were noted. Microscopically, the chorionic villi were enlarged and cystic. The diagnosis was "secundines, with suggestion of mole formation." One week later, the patient became nauseated and vomited. An A-Z test was positive. In spite of conservative therapy the symptoms persisted. A second A-Z test was positive. The uterus was enlarged to the size of a twelve-week gestation. A tentative clinical diagnosis of "choriomatous disease" was made and a hysterectomy and bilateral salpingo-oophorectomy were then performed. Grossly, the endometrial cavity was smooth throughout except for one area in the left side of the fundus, where a pinkish, mushy, shreddy material exhibiting vesicles and hemorrhagic areas was present. The latter mass extended through the entire thickness of the myometrium almost perforating the serosal surface. Microscopically (Fig. 7) sections showed destruction of the muscle by masses of trophoblastic cells amidst areas of hemorrhage and widespread necrosis. The cells were of two types, one with hyperchromatic, bizarre-shaped nuclei and acidophilic cytoplasm, the other, smaller cells with distinct borders and vesicular nuclei showing moderate variation in size, shape, and tinctorial properties and with an occasional mitotic figure. Several necrotic large acellular villi were present. Diagnosis: *Chorionepithelioma, low grade.* At present the patient is negative for metastases both clinically and radiologically.

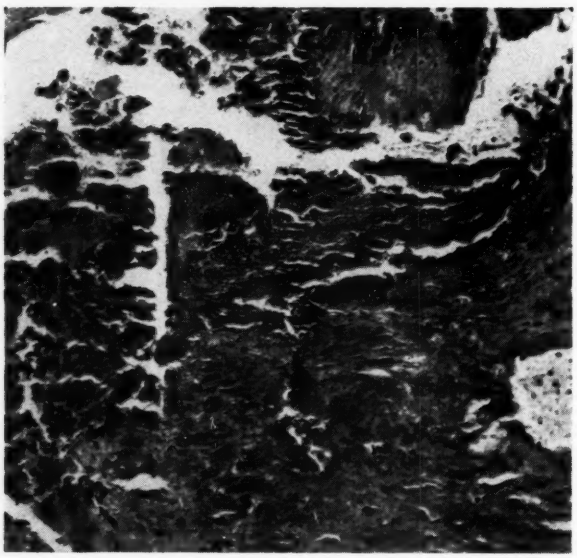

Fig. 7.—Case 8. Section of the uterus. A mass of trophoblastic cells, mainly syncytial in origin, is seen splitting the muscle bundles. All sections showed a predominance of the syncytial cells. Collections of Langhans' cells are also present. (×120.) Diagnosis: Low-grade chorionepithelioma of the uterus.

Comment.—The histologic picture is indicative of a destructive and neoplastic process. However, the lack of highly malignant-appearing cells, especially of the Langhans' variety, and the scarcity of mitotic figures places this case in the borderline group. The final diagnosis was *chorionepithelioma, low grade.*

CASE 9.—R. C., aged 40 years, gravida v, whose last regular menstrual period was Sept. 4, 1945, had a spontaneous abortion on December 31, followed by a curettage. The pathologic diagnosis was "secundines with acute inflammation." She continued to bleed vaginally and was curetted on Jan. 22, 1946. The vaginal bleeding continued and the uterus was boggy and enlarged to the size of a three-month pregnancy. On February 24, a second curettage was performed. Microscopically the curettings revealed chorionic villi showing very marked proliferation of both the Langhans' and syncytial cells. Numerous mitoses were present. A diagnosis of "chorionepithelioma" was made. X-ray of the lungs was negative and

a total hysterectomy and bilateral salpingo-oophorectomy were performed. Grossly, the uterus revealed a dark necrotic mass filling the uterine cavity. Microscopically, nests of large Langhans' and syncytial cells showing anaplasia and mitoses were seen scattered throughout the myometrium (Fig. 8). Necrosis and hemorrhage were also present. The pathologic diagnosis was *chorionepithelioma of the uterus.* At present, the patient is alive and well and clinically and radiologically negative for recurrence or metastases. *Final diagnosis: Chorionepithelioma of the uterus, low grade.*

Comment.—The Langhans' cells were not as pleomorphic as in previous fatal cases. Mitotic figures were scant in number.

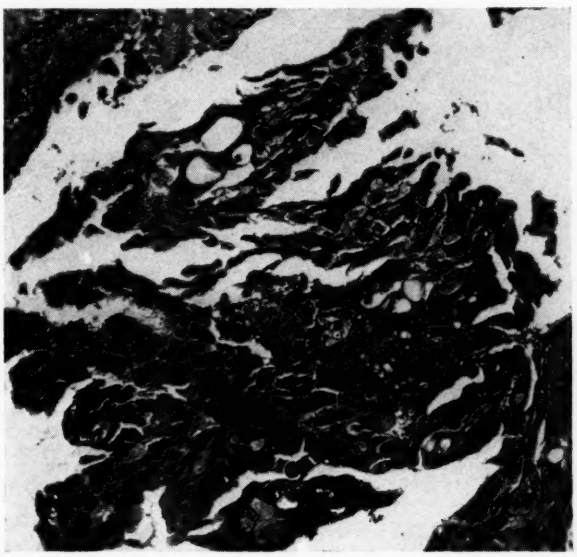

Fig. 8.—Case 9. Sections of uterus. The mass of trophoblastic cells is seen deep within the muscle layer. Both Langhans' and syncytial cells are identified and closely intermingled. Pleomorphism and variation in tinctorial intensities are evident. (×120.) Diagnosis: Chorionepithelioma of the uterus.

CASE 10.—B. W., aged 48 years, gravida ix, had a curettage on Jan. 9, 1939, because of history of passing vesicular-like tissue. On gross examination the curetted material revealed grayish translucent cystic nodules. Microscopically, the chorionic villi were greatly increased in size and showed a moderate degree of proliferation of both Langhans' and syncytial cells. Areas of hemorrhage and necrosis were frequent. No atypical changes were present. Diagnosis: *Hydatidiform mole with massive hemorrhage.* On January 13 the A-Z test was weakly positive. Patient continued to bleed vaginally. Examination on February 2 revealed enlargement of the uterus to size of ten-week pregnancy, and a positive A-Z test. The chest was radiologically negative. A panhysterectomy was performed. On gross examination of the uterus, within the posterlateral wall, there was a hemorrhagic polypoid mass which projected into the uterine cavity. This mass extended throughout the entire width of the myometrium reaching the serosal surface. Microscopically (Fig. 9) amidst areas of hemorrhage in the myometrium were seen masses of large irregular cells with bizarre-shaped, hyperchromatic nuclei showing a moderate number of mitoses. Some of the cells had distinct borders and were considered to be of the Langhans' variety; the majority, however, were syncytial cells. A number of venous sinuses were seen with clumps of syncytial and Langhans' cells in their lumen (Fig. 10). In addition, a diffuse scattering of isolated large syncytial cells were seen throughout the myometrium. A number of recently thrombosed veins were present. The diagnosis was "hydatidiform mole becoming invasive and showing early malignant changes." When last examined on Oct. 10, 1949, the patient was well and free of discernible metastases both clinically and radiologically. *Final diagnosis: Chorioadenoma destruens.*

CASE 11.—A. E., aged 26 years, gravida v, whose last menstrual period was April 8, 1947, had intermittent vaginal bleeding from July to November, when a mass of grapelike vesicles was passed. A curettage was performed. Gross examination revealed a large piece of tissue consisting of numerous pinkish-white cysts. Microscopically the chorionic villi were

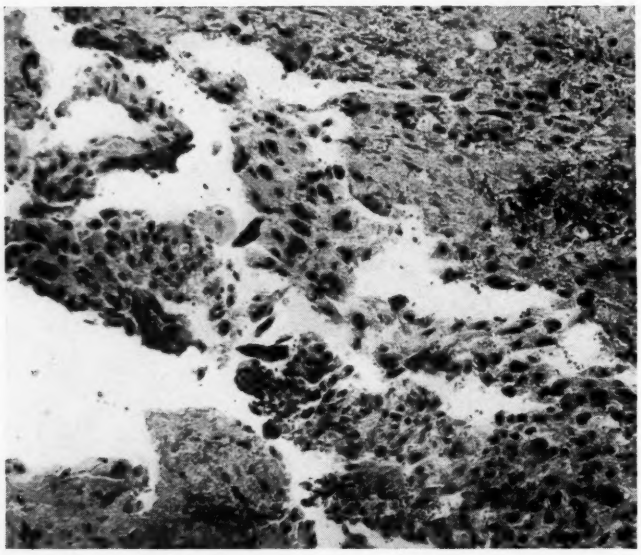

Fig. 9.—Case 10. Section of uterus. The mass of trophoblastic tissue splitting the muscle bundles consists of both Langhans' and syncytial cells, showing moderate degree of atypism. Mitoses are rare. In other sections the syncytial elements predominate. (×110.) Diagnosis: Chorioadenoma destruens of uterus, or low-grade chorionepithelioma.

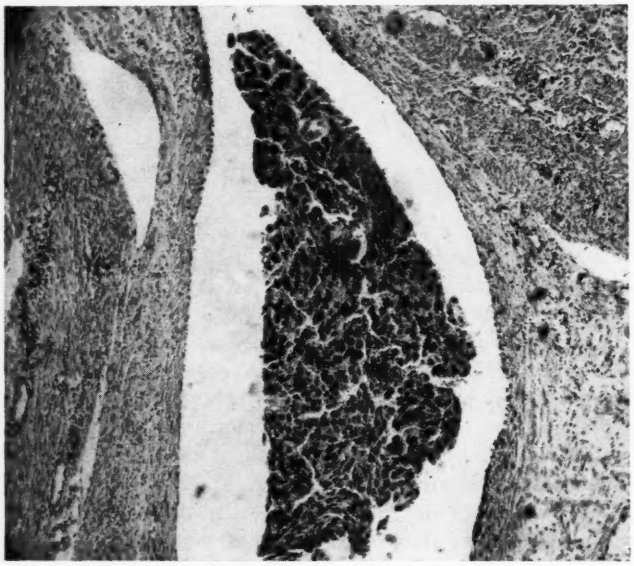

Fig. 10.—Case 10. Section of myometrium. An embolus composed of an island of trophoblastic tissue, mainly syncytial cells, with a smaller number of Langhans' cells lying free in the lumen of a vein. (×80.)

markedly enlarged with cystic edematous cores, and slight trophoblastic proliferation. Diagnosis: *Hydatidiform mole.* Patient continued to bleed intermittently, but her menses were considered to have returned. On Jan. 31, 1948, the A-Z test was negative. On March 20,

the A-Z test was positive. A total hysterectomy and bilateral salpingo-oophorectomy were performed. Grossly, a soft oval mass was present in the right cornual area of the uterine cavity. It was of pinkish-white color with a central hemorrhagic area. Microscopically (Fig. 11)

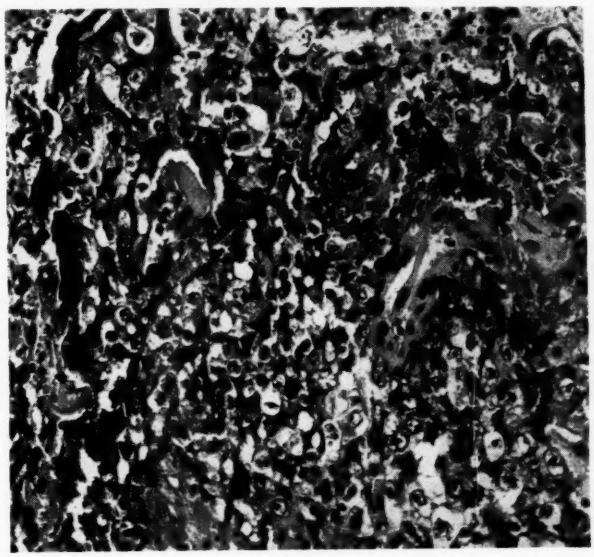

Fig. 11.—Case 11. Section of myometrium. Trophoblastic island deep within the muscle layer. The nuclei of the Langhans' cells show prominent nucleoli and a thick condensation of their chromatin network. The nuclei of the syncytial cells are markedly atypical. Mitoses are present and can be seen with hand lens. (×140.) Diagnosis: Chorionepithelioma of the uterus.

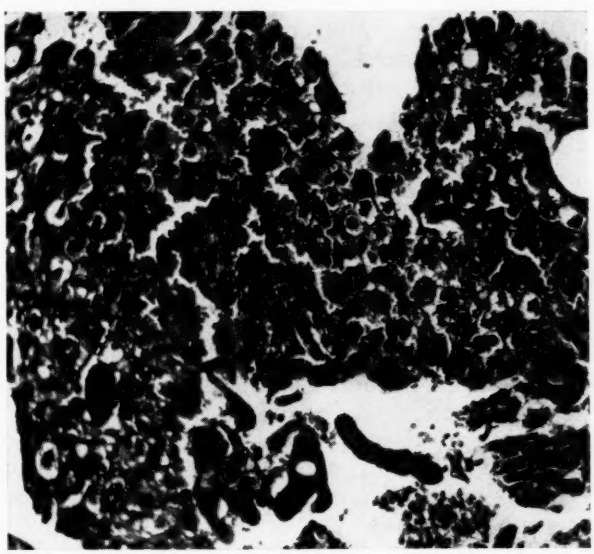

Fig. 12.—Case 12. Uterine curettings. The Langhans' cells show anaplastic changes. The nuclei are hyperchromatic and several mitotic figures can be seen (one in the center of the figure). The syncytial cells are seen as multinucleated giant cells or budding pseudoacini. (×220.) Diagnosis: Chorionepithelioma.

sections of the uterus showed numerous masses of tumor cells separated by areas of necrosis and hemorrhage. The Langhans' cells were arranged in mosaic fashion. Their cytoplasm was pale staining and their nuclei pleomorphic and showed a moderate number of

mitotic figures. The syncytial cells were arranged in anastomosing cords. Their nuclei were irregular, bizarre-shaped and hyperchromatic. The syncytial cells predominated. Angiomatous invasion was present. Diagnosis: *Chorionepithelioma of the uterus with angiomatous invasion.*

CASE 12.—C. H., aged 24 years, gravida i, whose last regular menstrual period was May 15, 1949, and who had had intermittent vaginal bleeding since June 24, had a curettage performed on July 3. Microscopically (Fig. 12) most of the sections showed large areas of decidual tissue with small islands of trophoblastic cells interspersed. The latter consisted mostly of compact layers of Langhans' cells in mosaic formation, the nuclei of which were vesicular, irregular, and showed mitoses. Sheets and anastomosing cords of syncytial cells with large, hyperchromatic, bizarre-shaped nuclei in an acidophilic cytoplasmic mass were seen at the periphery. Only two chorionic villi were found in all tissue received and they revealed degenerated centers and moderate trophoblastic proliferation. Vascular channels contained trophoblasts. Diagnosis was *chorionepithelioma of the uterus.* Two weeks later, A-Z test and chest x-ray were negative. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus failed to reveal any further evidence of tumor or pregnancy. On July 30 and August 30 chest plates and A-Z tests were negative. *Final diagnosis: Chorionepithelioma of the uterus.*

Comment

Incidence.—Reports as to the incidence of chorionepithelioma are extremely variable, ranging from 0.019 per cent[11] to 3 per cent,[12] and that of malignancy of hydatidiform moles from 1.3 per cent[7] to 50 per cent,[13] depending upon the criteria used by the various authors. Novak, in a study of 48,000 gynecological cases, reports that he has not had more than 8 or 9 genuine chorionepitheliomas. He states that not more than 1 per cent of moles actually become malignant. One of us (J.M.R.) found 2 cases of chorionepithelioma in 10,301 gynecological cases, an incidence of 0.019 per cent. Mathieu[5] reports an incidence of 9.4 per cent malignancy in a study of 127 moles. Chesley[14] reports an incidence of mole as 1 in 1,321 deliveries and that of malignancy of mole as 5.3 per cent.

Age and Parity.—In our cases the age range was from 19 to 48 years. It may occur at any age between the menarche and the menopause or even after the menopause, since the disease is known to have a latent period of many years following a pregnancy. The multipara is more susceptible to choriomatous formation than the primipara.

Early Diagnosis.—The most commonly accepted figures are that 50 per cent of chorionepitheliomas follow a hydatidiform mole, 25 per cent a full-term pregnancy, and 25 per cent an abortion. When the diagnosis of mole is made, the uterus should be emptied immediately, preferably by the vaginal route. When a patient is found to have a large mole, particularly when she has had many children or is near the menopause, hysterectomy is the treatment of choice. The subsequent close observation of the patient is of prime importance. The patient must report for periodic examinations every two weeks for three months, then once a month for the next nine months, and then quarterly for the second year, and to bring a morning urine specimen at each visit. The patient is questioned as to the presence of vaginal bleeding, hemoptysis, or chest symptoms. A pelvic examination is done, since an enlarged subinvoluted boggy uterus is a frequent finding associated with chorionic diseases. The Aschheim-Zondek test may remain positive for eight weeks following the removal of the mole. Therefore, qualitative tests are of no value. Thus quantitative tests are performed during the first eight weeks following the removal of a mole. Subsequently, qualitative tests are used, and if the latter are positive, repeated quantitative tests are performed. In addition, a diagnostic curettage should be done

promptly if there is persistence or recurrence of vaginal bleeding and/or a positive Aschheim-Zondek test following a full-term pregnancy, abortion, or especially a mole, after the possibility of intervening pregnancy has been excluded.

The Aschheim-Zondek Test.—The A-Z test is indicated in the following situations:

1. Recurrence of vaginal bleeding following a full-term pregnancy, abortion, or removal of a hydatidiform mole.

2. Following the complete expulsion or removal of a hydatidiform mole, for which periodic tests are indicated. Repeated quantitative estimations of chorionic hormone are the only means for the early detection of chorionepithelioma following a mole. A single positive test, even months later, is of no value. So long as the titer is decreasing or at least remaining constant, watchful conservatism may still be applied. If a malignant change does occur, there is usually a sudden abrupt rise in the hormone titer, and if the development of a new pregnancy can be ruled out the diagnosis of chorionepithelioma is indicated.

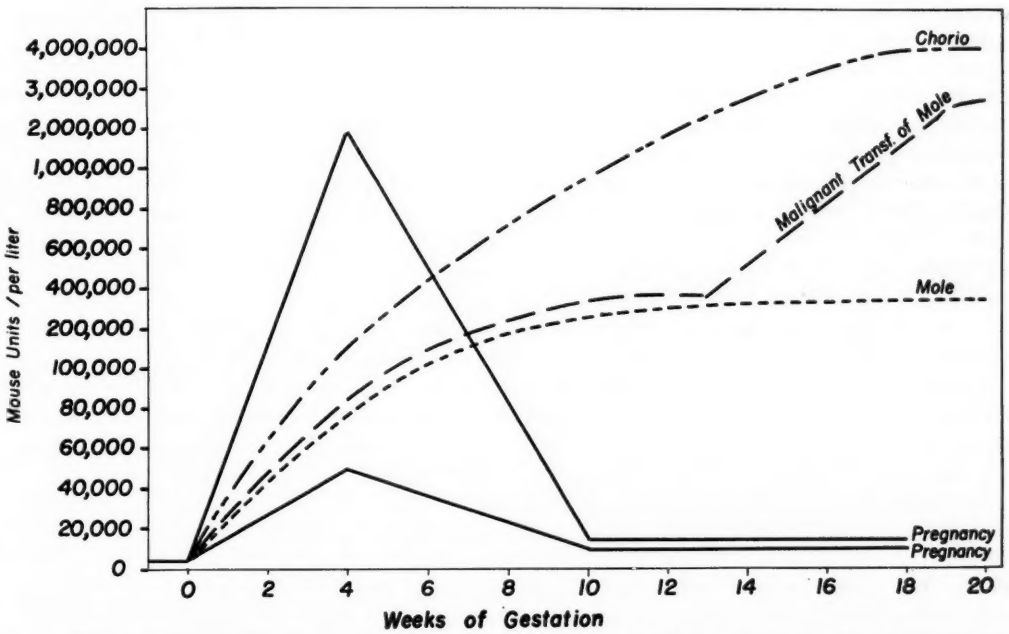

Fig. 13.—Composite graph of urinary excretion of chorionic gonadotrophic hormone in normal pregnancy, hydatidiform mole, and chorionepithelioma. (From averages of Zondek, Browne, Evans, Smith, Randall, and Siegler.)

3. Periodic A-Z tests should be performed to evaluate the prognosis after surgical removal of a proved case of chorionepithelioma.

The biologic tests are not infallible. Values comparable to those found in mole or chorionepithelioma have been reported in normal pregnancy. Thus a single test is of no value in differentiation of the transient peak of pregnancy. However, repeated quantitative tests over a period of two to four weeks will usually clarify the situation.

On the other hand, low values and at times even negative tests have been reported associated with mole and chorionepithelioma. The following reasons have been advanced to explain the negative reactions:[15] (1) refractoriness of

the animal employed in the test; (2) the presence of only very small nodules showing low proliferative activity; (3) deficient absorption of the gonadotrophins due to thickening of the adjacent connective tissue; (4) necrobiosis or degeneration of the growth; (5) insufficient renal filtering or destruction of the chorionic gonadotrophins at the level of the latter; the negative phase may only be temporary but in some cases persists for long periods; (6) the characteristic destructive action of the trophoblastic elements upon the surrounding tissues, causing loss of contact of the growth with the maternal circulation; (7) complete blockage of the maternal vessels about the growth by tumor thrombi and emboli, not allowing the hormones to reach the general circulation.

Interpretation of Findings at Curettage.—Since the fragments of tissue have been forcefully separated from their surroundings, the time-honored criteria of invasion and destruction of the underlying tissue are of no great help. The pathologist must arrive at a diagnosis by study of the general architectural pattern and a search for atypism or malignancy in the individual cells.

If a well-preserved villous pattern with minimal trophoblastic proliferation is present, or if large masses of trophoblastic tissue, showing definite evidence of anaplasia, are found, the diagnosis is simple. In between the two possibilities, any combination of patterns may exist. Many observers are of the opinion that when well-preserved villi are present one should certainly lean backward in the diagnosis of chorionepithelioma. This has not been our experience, since in two of our fatal cases, well-preserved villi and masses of anaplastic trophoblastic tissue were present in the same section. We believe that the qualitative or atypical changes of the individual cells, and especially their nuclei, constitute the most reliable guide to malignant potentialities. Thus it is the disparity in size and shape, hyperchromatism instead of pyknosis of the syncytial cells and pleomorphism of the Langhans' cells with mitoses, that makes for malignancy.

A certain number of chorionepitheliomas develop beneath the mucosal surface within the uterine wall or may be entirely extrauterine, and therefore inaccessible to the curette. Besides, errors in histologic diagnosis are not uncommon even in the hands of competent pathologists, as considerable experience and extreme care in this particular field of histopathology are required. Hertig and Sheldon,[17] from a general consideration of the data on 200 hydatidiform moles, show that there is a general correlation between the morphologic appearance of the original specimen and/or the curettings, and the subsequent development of some grade of chorionic malignancy. Many authorities state that the histologic differentiation of typical syncytial reactions from true chorionepithelioma is frequently difficult and often the distinction can be made only on the basis of gonadotrophic hormone studies. If one would therefore pause to correlate the clinical, microscopic, and biologic findings, many errors and much delay would be avoided in arriving at a diagnosis of chorionepithelioma.

Extension and Metastases.—Chorionepithelioma behaves like a sarcoma. Its inherent tendency to invade the blood vessels and its local invasive and destructive nature assert themselves quickly and account for the widespread dissemination. The broad ligament structures, including the ureter and not infrequently the tube and ovary, may be invaded. The cervix and bladder are involved more often than is generally realized. Vaginal and vulvar metastases have been recorded. They appear as isolated dark-red or bluish raised nodules which resemble an old hematoma and on section give the appearance of a blood clot. Distant metastases are hematogenous and involve most frequently the lungs, brain, liver, and kidney, in above order of frequency.

Course and Prognosis

Because of the uncertainty and confusion over the histologic diagnosis of benign and malignant choriomatous lesions, isolated reports and statistics about the eventual outcome of the mole and chorionepithelioma are not of great value. This must be kept in mind when confronted with apparent incongruities in reports of complete regression of a malignant lesion or of a fatal outcome in an alleged benign mole.

Of the 12 cases in this series:

1. Eleven may be classified as chorionepithelioma of varying degrees of malignancy: (a) Six died within seven to thirty months after the removal of the original mole or onset of symptoms of the disease. (b) Five are still alive and free from any discernible clinical signs or symptoms of the disease and have negative A-Z tests from four to fifty-two months following the initial removal of the mole.

2. One patient who had chorioma destruens or malignant mole is alive and has been clinically and biologically free of the disease for ten years following initial removal of the mole.

The small group of cases reported in the literature which exhibit regression and spontaneous cure, not only in the primary tumor but also in the metastasis, should be considered the rare exception.

Two explanations have been advanced for this regression and spontaneous cure. First, that the maternal tissues, presumably through the agency of the decidual cells, exhibit a defensive mechanism which holds the trophoblastic encroachment within normal limits. A deficiency in this defensive mechanism may be more important than the abnormal trophoblastic activity which characterizes the so-called malignant mole.[18]

Second, that some lytic substance might be a factor in the remissions of chorionepithelioma. This is based on the fact that the majority of pregnant women have living chorionic cells in their blood circulation, and that after delivery this lytic or "x" substance destroys the chorionic tissue.[19]

Treatment

Early diagnosis of chorionepithelioma is of utmost importance. To be conservative in the treatment of chorionepithelioma, one must be radical. All patients should be operated upon as soon as the diagnosis is made, since it has been shown that the death rate increases directly in proportion to the delay in diagnosis and treatment. A total hysterectomy and bilateral salpingo-oophorectomy must be performed regardless of the age of the patient. All possible avenues whereby viable cells may be disseminated by manipulation are occluded. This is accomplished by preliminary suture of the lips of the cervix and clamping of the vascular area beside the uterine horn on each side. *A uterine elevator of the nontoothed variety is used.* The operation should be followed routinely by a course of irradiation. Periodic Aschheim-Zondek tests should be done. The authors admit that in a few cases the uterus may be needlessly removed, but this should not influence one's choice of early operative interference.

When metastases are present, is surgery justified? If the metastases are located solely in the pelvis or perineum, a panhysterectomy and surgical extirpation of the metastatic nodules, wherever possible, should be performed. If the nodules are surgically inaccessible, they are to be treated by irradiation.

When distant metastases exist, irradiation is the treatment of choice in most cases. Some feel that irradiation is of value when the patient has an inoperable

growth or when the surgical risk is too great. Others believe that irradiation should be used in addition to operation either pre- or postoperatively in as large dosage as can be tolerated. Recently[20] large doses of estrogens have been used upon the primary as well as the metastatic tumor and have been found to alleviate some of the symptoms.

Summary and Conclusions

1. Eleven cases of chorionepithelioma and one of destructive mole are presented, with fatal termination in six, the remaining six being alive and free of any discernible clinical signs or symptoms of this disease, as well as giving negative biological tests from four months to ten years following the initial removal of the mole. Just as in other tumors, different grades of malignancy of chorionepithelioma do exist, which may explain the variations in their clinical course. The rare cases of regressions and spontaneous cures of the primary or secondary lesions may be explained by the lytic factor, or by the unusually protective action of the decidual cells.

2. The choriomas are classified accordingly into four groups: (1) hydatidiform mole, (2) syncytioma and syncytial endometritis, (3) destructive mole, and (4) chorionepithelioma.

3. The incidence of malignant change in hydatidiform mole varies according to the thoroughness of study and the histologic criteria used. From accumulated statistical study it would appear that the incidence is 5 per cent.

4. Chorionepithelioma may occur at any age between the menarche and the menopause or even after the menopause.

5. The multipara is more susceptible than the primipara (3:1).

6. The Aschheim-Zondek test is of significant value, but certain pitfalls exist which must be evaluated. (See Cases 1, 3, 6, 11.) For the first eight weeks following a mole, the quantitative test is used. After this period or in isolated instances the qualitative pregnancy test is employed. If it becomes positive, repeated quantitative tests are performed.

7. The difficulties of interpretation of curettings are discussed and the importance of qualitative changes is emphasized. The observation that a negative curettage is possible even in the presence of a chorionepithelioma is explained.

8. Clinical, pathologic, and biologic data must always be correlated and each case is to be individualized.

9. Once the diagnosis of chorionepithelioma is made, immediate surgery is indicated. When the lesion is confined to the uterus, a panhysterectomy and bilateral salpingo-oophorectomy are to be performed. If local lesions are present, they are extirpated surgically, if accessible; if not, they should be irradiated. If distant metastases are present, irradiation is the treatment of choice. Postoperative irradiation and follow-up of the patient with periodic A-Z tests are mandatory.

10. Early diagnosis is of prime importance. The highest percentage of cures will be obtained when there is judicious correlation of the clinical history, meticulous histologic study, and intelligent interpretation of the biologic pregnancy tests.

Due to limitation of space, this paper has been abbreviated as originally presented.

The authors wish to express their appreciation to Drs. H. Berman, S. Brody, F. Epstein, G. Gorham, J. Liswood, and C. Weitzman for their kind permission to use the clinical data of some of the cases, and to Drs. A. Coblenz, M. J. Fein, and A. Kantrowitz for some of the pathologic material.

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Discussion

DR. J. EDWARD HALL.—It is most unusual for 12 cases of chorionepithelioma to be reported in one paper, and because it is unusual, one should be very analytical of the material presented. These patients were all distributed over a period of only 10 years, and 7 of them were seen within a 2-year period. The authors have failed to give the number of deliveries during this period, but gave figures from other sources. At the Brooklyn Hospital in a 20-year period there were only 2 cases of chorionepithelioma. During this time we had 24,318 deliveries. At the Margaret Hague Hospital in Jersey City, in 75,000 deliveries there were only 3 cases, a ratio of 1:25,000. If we project these figures into the cases presented here for a 10-year period, there should have been approximately 150,000 deliveries in the institution from which these cases are reported, or 15,000 deliveries a year, which is a high figure.

As has been stated, the hormonal tests are not infallible and in addition to the points mentioned in the paper should be added the high levels of chorionic gonadotropin hormone sometimes present in some cases of toxemia of pregnancy. This must be borne in mind in arriving at a differential diagnosis. The levels that the authors used as a criterion were not given. Zondek stated that at least 200,000 units per liter should be present before a diagnosis of mole should be made.

I want to emphasize the difficulty of making a diagnosis of this condition from curetted material. Even normal embryonal tissue may present a bizarre appearance. Syncytial endometritis offers another difficult diagnostic problem, especially if myometrial elements are obtained with the curettage.

Once the diagnosis is established, the treatment is as stated by the authors. Some uteri may be removed and the presumptive diagnosis proved to be wrong, but if all the

evidence suggests chorionepithelioma, one must be radical in the therapy, even if some uteri are unnecessarily removed and are proved normal.

I would like to ask the authors to clarify one of their statements, namely, that "When distant metastases exist, irradiation is the treatment of choice." Do they mean irradiation to both the primary and secondary growths or only the secondary? Personally, I would prefer to remove the primary growth, if possible, and give irradiation to the secondary growth.

A fatal termination is to be expected in about 80 per cent of all cases of this disease, even in the best hands. Ewing stated that he had been unable to find any record of operative cure in a proved case of chorionepithelioma. Novak states, "When one meets with reports of high percentages of cures, one must of necessity question the validity of the pathological diagnosis, especially in view of the difficulties involved in the proper evaluation of many cases." However, 6, or 50 per cent, of the patients reported here tonight are alive and apparently free of any chorionepithelioma. Nevertheless, the authors state in their original manuscript, "In genuine cases of chorionepithelioma, a fatal termination is to be expected in the majority of cases." In reviewing the written description of these cases there are several whose microscopic findings would suggest a doubt as to the diagnosis, and because of the high percentage of cures in this report, one should raise the question whether these were all genuine malignancies. I grant that reading a report or hearing one given is not the same as seeing the material, and all the diagnoses made may be absolutely correct, but one must be certain of the diagnosis in order to rule out any criticism when a paper is published.

I would like to say a word about hydatidiform mole and its relationship to hydatid degeneration of chorionic villi. As more and more material obtained from abortions is studied, one is impressed with the frequency of hydatid degeneration. This is, however, far removed from the fully developed hydatidiform mole. The two may be related, but I do not believe the common hydatid degeneration seen in such cases need be feared as one does the full-blown hydatidiform mole.

DR. RAVID.—To answer some of the questions raised by Dr. Hall: First, in regard to the incidence of this condition. Although it might appear rather unusual for three observers to present 12 cases even in the course of their lifetime, nevertheless this may be explained simply by the fact that these cases were accumulated from *five* different hospitals. In one hospital alone, where I had served as pathologist for 14 years, we observed only two such cases. There was a third case there, in which all the clinical and endocrinological findings pointed to a chorionepithelioma, but where no final pathologic evidence could be obtained. In this 14-year period there were, in the same hospital, about 20,000 gynecological specimens removed at operation and about 90,000 babies delivered. Therefore, if you were to make a cumulative statistical study of all the gynecological and obstetrical cases in these five hospitals, I am certain that you would find the incidence of chorionepithelioma in our series to be very close to that cited in the literature.

The point brought out by Dr. Hall regarding the difficulties in the histologic diagnosis of this condition is a very important one. For this very reason, our review of these cases was made in a most objective manner. First, the pathologic material and particularly the slides were very thoroughly studied, and a diagnosis was made on purely histologic grounds.

After a thorough study of these cases, especially from a retrospective point of view, we came to realize that there is still a great deal that we must learn about the criteria to be used in the histologic diagnosis of choriomatous disease.

All the cases in our series, as I pointed out before, were reviewed in correlation with the clinical aspects and follow-up study. Thus, one of the cases which I classified about ten years ago as a low-grade chorionepithelioma had to be reclassified as a "chorioadenoma destruens" with early malignant changes, in the light of our present retrospective study. On the other hand, several cases which were originally diagnosed by others as benign moles

must now, after thorough study of the same histologic material, be reclassified as malignant. Thus there is a great deal to be learned about the histologic appearance of choriomas. It is only by correlating the histologic picture, the hormonal findings, and the ultimate course, that we may be able to arrive at a better understanding of this problem. Thus, at times, we are obliged to modify or even reverse our original anatomic diagnosis in light of what ultimately happens to the patient after many years of careful observation.

Choriomas behave in an entirely different manner from that of other neoplasms. Thus, vascular embolization by trophoblastic elements and widespread invasion of the myometrium even to the extent of its almost utter destrucation—the two cardinal signs which characterize all malignant growths—may not at all be indicative of malignancy as far as chorionic disease of the uterus is concerned, for this may be observed even in normal pregnancy and especially in a destructive mole. It is the finer and minute qualitative cellular changes within the trophoblastic elements themselves, rather than in their host, that are of utmost importance in the correct evaluation of the pathologic process in question. When analyzing the chorionic villi of a given mole, the appearance of their component cells, and especially the Langhans' variety, is of prime importance. Thus, when the latter show variation in size and shape, and pleomorphism and hyperchromatism of the nuclei, with complex scattering of the chromatin, and, above all, mitotic figures—the diagnosis of malignancy or at least of malignant potentiality must be made, all other considerations notwithstanding.

Similar qualitative changes may at times also be detected within the syncytial cells, but these are more difficult to evaluate. On the other hand, if no such changes are found, and, provided that a sufficiently large number of sections have been taken, and most carefully studied, the lesion must be called benign. Furthermore, all curettings must be carefully examined for the presence of unusually large villi which should make one suspicious of a mole, even though no such possibility suggested itself on gross examination. I am certain that if all these precautions are heeded fewer errors in the proper diagnosis of chorionic disease will be made.

I agree with Dr. Hall that, before labeling a choriomatous lesion malignant, we must have definite histologic proof to back it up. When such cases are reported in the literature there should be sufficient photomicrographic evidence to support such diagnosis.

It is our chief aim by this presentation to stimulate further study and investigation of this extremely important problem which is still within the realm of preventive medicine.

DR. SIEGLER (Closing).—Our technique of the quantitative A-Z test is that of Kolmer and Boerner. Briefly, it consists of injecting groups of five mice with six doses of 0.5 c.c. each of urine diluted in 1:10, 1:50, 1:100 and 1:1,000. The technique is the same as for the qualitative test. If the dilution of 1:10 gives a positive result, then no less than 3,300 mouse units of hormone are assumed to be present per liter of urine, with corresponding higher values, if the higher dilutions give positive results. One must also take into consideration, when making such quantitative determinations, that a very high degree of hormone content is present at about the sixtieth day of normal pregnancy, but it is the increasing amount of chorionic gonadotrophic hormone which is important in the diagnosing and following cases of hydatidiform mole and chorionepithelioma. Quantitative assays for chorionic gonadotrophic hormone need to be done only following its detection by qualitative tests.

Regarding Dr. Hall's comment as to treatment, we advocate panhysterectomy with bilateral salpingo-oophorectomy in every case wherein a diagnosis suggesting chorionepithelioma is made clinically, histologically, and biologically. It is true that a small number of uteri might be saved by a more conservative approach in the evaluation of histologic criteria of chorionepithelioma. It seems to us, however, that since the malignant potentiality of hydatidiform mole is about 5 per cent, and since no one can determine the time when a primary growth might give rise to metastases, or when, in an occasional instance, retrogression of the disease will occur, and since malignant choriomas or choriocarcinoma usually

means death to the patient, it is obvious that the sooner the treatment is instituted following diagnosis, the lower will be our mortality rate.

Regarding Dr. Hall's comment as to metastases, it is generally conceded that, in most instances, the removal of the primary growth may result in retrogression of the metastases. Localized pelvic metastases, however, should be surgically removed at the time of the hysterectomy, if it is at all feasible. In the inoperable cases, or extensive metastatic growth, adequate irradiation offers the best prognosis. Brunschwig has reecntly advocated, in these inoperable cases, the complete removal of the pelvic organs with transplantation of the ureters into the colon following irradiation. Of late, large doses of estrogens have also been used in these cases, with the temporary alleviation of some of the symptoms.

With regard to the end results of the twelve cases reported, six patients died in periods varying from three months to two and a half years after the initial expulsion of the mole, the latter having had no histological evidence of chorionepithelioma in the endometrial curettings or the uterus at the time of death, although chorionepithelioma was found in the lungs. Of these cases, since death had occurred, there seems to be no question as to the final diagnosis of choriocarcinoma. Of the remaining six, one was subsequently classified as chorioma destruens, this patient being alive ten years following the expulsion of the mole. Two patients are alive four and a half years, one, twenty months, sixteen months, and four months, respectively, following the expulsion of the mole. It is true, as has been commented by Dr. Hall, that very frequently there is a lack of unanimity of opinion with regard to the histological interpretation and classification of choriomas, and that both Novak and Ewing state that most patients with genuine chorionepitheliomas do not live. It is our impression, however, from this study, that there are several grades of malignancy of this disease, and our procedure as to treatment should be similar to that of carcinoma, whether it be grade I or grade IV, or that of preinvasive carcinoma of the cervix. It is also our impression that in those instances where a diagnosis of the disease was made early and hysterectomy immediately performed, the patient was apparently cured, and where the diagnosis was delayed, the disease being of long standing, death occurred in most instances.

THE EMOTIONAL ASPECTS OF OBSTETRIC AND GYNECOLOGIC DISORDERS*

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DURING the past decade a significant shift has been perceptible in the attitudes of many leading gynecologists and obstetricians toward psychosomatic problems. When references to the psychogenic origin of certain female disorders first began to appear in the literature, the reception accorded them could hardly have been characterized by either tolerance or scientific understanding. It is, therefore, an encouraging observation that today we are witnessing not only an increase in the number of such contributions (Kosmak,[1] Cooke,[2] Taylor,[3] Deutsch,[4] etc.) but a progressively more constructive reaction to them, as evidenced by the editorial comments of Eastman[5] and Novak[6] in the *Survey*, and Greenhill[7] in the *Yearbook*.

A doubt no longer exists whether psychiatry is deserving of a place in the field of obstetrics and gynecology. The only question to be resolved is how its important principles can be more widely and successfully applied through a program of integrating the related subject material. Already most alert practitioners recognize that a large proportion of women seeking aid for *female trouble* are instead *troubled females*.

The incidence of psychosomatic disorders in the obstetrical and gynecological population has been variously estimated in the neighborhood of 30 to 70 per cent. However, due to the delicate balance and complex integration of the psychologic and physiologic processes of the female reproductive system, one can reasonably assume that almost every woman will at some time develop a psychosomatic pelvic disturbance. This may vary in degree from an occasional delayed period to the most protracted amenorrhea or menometrorrhagia, and it is for this reason that we believe it to be the responsibility of every physician engaged in this specialty to become familiar with the problem. No other approach can hope effectively to reduce both the great number of pelvic operations unnecessarily performed and the large quantity of hormones irrationally employed (Miller,[8] Weaver[9]).

The purpose of this preliminary report is to describe the growth of a project which began several years ago and which has resulted recently in the establishment of a psychosomatic obstetrical and gynecological clinic, the first to function in this country, we believe, as a unit within the gynecological and obstetrical departments. This is as it should function, for manifold reasons, not the least

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of which is that we had long observed in private practice the unconscious tendency for patients to disrobe emotionally when the therapeutic setting had been made sufficiently comfortable. In the clinic, especially, there are many advantages to this procedure over the customary policy of referring patients to the psychiatric department for consultation. In the first place, having a physician oriented in both specialties, available within the department at all times, expedites the investigation. Second, it eliminates the patient resistance to the implication that "something is wrong with her mind"; regardless how subtle the explanation is made, many patients are reluctant to be classified as, or to share a waiting room with "mental cases."

Last year we noted with interest the report from England by Snaith and Ridley,[10] who conduct their work as a separate psychiatric unit within the gynecological clinic. While this system also obviates the disadvantages of referring patients out of their own clinic setting, there is lost, we feel, some of the rapport originally developed with the attending physician. This rapport may never be fully regained with the psychiatrist, and, regardless, much valuable time and contact with the patient may be lost in making the change. We are furthermore convinced that these psychosomatic disturbances require a broader background than is generally within the scope of the average psychiatrist, since they demand a basic understanding of the sensitive reproductive and cyclic endocrinological physiology of the female, which is more properly in the gynecologist's domain.

In no way have we intended to discredit the role of the psychiatrist in our program. On the contrary, his aid is considered so important that we cannot reconcile the waste of these services with so critical a shortage for the routine psychosomatic approach. From our experience we are convinced that this routine work-up can be adequately performed by any interested and well-indoctrinated physician—reserving the assistance of the psychiatrist for those individual patients who require more thorough investigation and definitive treatment.

The goals of this program are essentially twofold. First, to evaluate the psychogenic factor in the patient's complaint; second, to provide, when indicated, that degree of psychotherapy which is practicable in the clinic setting. It will be observed from this report that these two functions cannot be separated, since therapy begins with the original interview and results from the development of a healthy interpersonal relationship between the patient and the doctor.

The Principles of the Psychosomatic Approach

All patients in our clinic are studied in the following manner:

1. Routine medical history, physical examination, and laboratory work-up.
2. Gynecological history and pelvic examination.
3. Psychosomatic interviewing when the examination fails to disclose sufficient structural pathology to account for symptomatology.

One cannot stress too emphatically the importance of a genuinely interested, tolerant attitude on the part of the physician. We believe that clinic patients

suffer more often from the lack of opportunity to be heard, than from any major neglect of adequate physical investigation. It is inconsistent, therefore, with the accepted policy to be contemptuous or abrupt, since this defeats the desired aim of encouraging maximum patient-self-expression. Free ventilation of areas of anxiety and tension is the cornerstone of our program, but effective therapy must embrace not only the management of anxiety but also the many defenses erected by the individual against anxiety. We are particularly interested, moreover, in knowing both the patient's attitude toward the illness and her interpretation of the meaning of her symptoms. The value of inquiring carefully into the *concept of meaning* of the illness rather than probing blindly for the cause (Whitehorn[11]) was well demonstrated in a woman referred to the clinic recently because of abdominopelvic pain and urinary stress incontinence.

In less than a half-hour interview we learned that this 42-year-old woman had been ill for about fifteen years. Because of a contracted pelvis, she had been delivered of a full-term female infant by cesarean section nineteen years previously and had been warned not to become pregnant again. Nevertheless, two induced abortions followed in the next three or four years, from which there were no immediate complications. Further direct questioning was resisted, the patient stating, "I have a perfect husband and daughter and have no worries, financial or otherwise, so please don't tell me it's my imagination," referring to the diagnosis often made by her physicians. Despite her protests, she appeared anxious, agitated, rigidly defensive, and reluctant to answer direct questions. Accordingly, she was instructed to simply tell us her own interpretation of the illness, which revealed these facts.

The onset of abdominal and pelvic discomfort began shortly after the second abortion and was described by the patient as "a pain which traveled about the pelvis and abdomen." *This she attributed to products of conception that had never been properly removed.* Considerable guilt was associated with the sin of having destroyed the pregnancy. Most of her complaints involved the body excretory functions and included statements that "defecation left her weak and exhausted," "urination was painful, malodorous, and at times uncontrolled," and "monthly bleeding was red and green, hardly to be called menstruation." Intercourse was not pleasurable to her but was engaged in as a wifely duty. She bemoaned her loneliness, saying that she had never known the love of a mother. When she was 1 year old, her father died; when she was 9, her mother died, after which she was raised by a very strict aunt. For years the patient had been a neat and orderly person, running a perfect home. Lately, however, she had become careless and less concerned with her house; in fact, her husband now accused her of being lazy and disinterested. Before the end of the interview, she admitted to attacks of melancholic depression, frequent crying spells, ideas of suicide, feelings of bewilderment and uselessness to the family, intense guilt dating to the abortions, and bizaare descriptions of dripping sensations from the brain into the abdomen.

The pelvic examination of the patient revealed no structural pathology. Apparently we were dealing with a psychotic depression, and, for the same problem, her left tube and ovary had been removed in another hospital a year before without relief; on the contrary, the complaints were now more exaggerated than ever.*

Such errors in diagnosis and treatment will be repeatedly made unless the physician learns to evaluate the patient as well as her symptoms. "Sizing up" a patient is an ability that one acquires with experience, but again we must point out that, in the beginning, patience and an acute ear for listening are the basic equipment required.

*We have since learned that this patient had several other exploratory operations, in addition to 14 electric shock treatments administered during 11 weeks' hospitalization in a state mental institution to which she had been committed from the Out Patient Department, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital.

From the very onset of our project, certain significant observations have been made, through the use of this "talking-out" technique (catharsis):

1. A fairly rapid transference of dependence to the therapist despite the spacing of visits at weekly intervals. This we believe is in direct relationship to the degree of acceptance perceived by the patient.
2. A gradual decrease in the patient's tension and anxiety, evidenced by a more cheerful, optimistic attitude at subsequent visits.
3. A rather early shift of complaints away from the pelvis, and directed toward disturbing problems of the immediate life situation, i.e., parents, children, husband, housing, finances, occupation, and sex. It has been strikingly noted that during repeat visits the patient does not request nor do we suggest pelvic examinations.
4. Diminution in the intensity or complete relief of somatic symptoms after a few interviews, except in the deeply rooted neurotic women, where symptoms have long served as a defense mechanism or for secondary gain.
5. The likelihood of recurrence of the old symptoms or the development of new ones, unless insight has accompanied improvement.
6. The frequence with which serious sexual disturbances accompany these disorders and the relatively rapid improvement resulting from the correction of the sexual problems.
7. Real personality changes can be accomplished only by definitive treatment which requires a long, educational process aimed at emotionally maturing the patient.

We have no illusions to the extent of believing that a patient can be fully analyzed through weekly therapeutic sessions. But neither do we consider complete analysis an essential part or an immediate goal of our program. While the depth of therapy employed in our clinic is not exaggerated, we deem it necessary, nevertheless, to distinguish this form of *brief therapy* from the so-called *superficial therapy*. Our objectives are as yet quite modest, but in addition to ventilation and supportive reassurance, an honest effort has been made to attempt re-education just as soon as any degree of insight is accepted by the patient. For this purpose we have found the Finesinger technique of psychiatric interviewing[12] adequate to our needs in most instances. Freudian analytic concepts, including dream analysis, are employed when applicable, and that knowledge is regarded as an immeasurable asset to the therapist. Moreover, every available adjunct is utilized to assist the patient in working through her difficulties, and these include sedation, hormones, social service, public welfare, occupational and physical therapy. At times, each has played an integral part in the required treatment program. Where serious sexual incompatibility is uncovered, the husband is often invited to the clinic for discussion, though too often he prefers to keep a reasonable distance between us.

During the period of our investigation, we have seen the entire gamut of pelvic psychosomatic disorders, including vaginismus, dyspareunia, frigidity, premenstrual tension, dysmenorrhea, amenorrhea, menometrorrhagia, pseudocyesis, sterility, abortion, hyperemesis gravidarum, chronic pelvic pain and backache, urinary incontinence and retention, diarrhea and constipation, pathological labors, and the menopausal syndrome. While Dunbar[13] has attempted to profile these women into specific personality types, whose conflicts are expressed by either frigidity, dysmenorrhea, or the abortion habit, etc., we have been more impressed with the likelihood of these women to develop, within a short period of time, any or many combinations of the above disorders. The only fairly constant denominator observed by us has been the immature, de-

pendent personality of the patient. This trait may often be masked by a deceivingly aggressive, dominant drive, yet we have generally been able to demonstrate that, under the transparent facade, rests an emotionally immature individual, groping endlessly for acceptance and security. Shorvon and Richardson,[14] in describing a series of patients with sudden obesity and menstrual disturbances precipitated by psychological trauma, comment that immaturity, impulsiveness, and poorly organized emotional life were common to all of their patients. Rubenstein,[15] recently, in psychoanalyzing five women referred because of functional sterility, found in all of them evidence of deep-seated hostility to mother. He acknowledged, however, that this finding is too commonly present in many multiparous women to ascribe specific significance to it.

The Dynamics of Pelvic Psychosomatic Disorders

The work of Selye,[16] Harris,[17] Friedgood,[18] and Hume[19] has given us a feasible basis for understanding the dynamics through which disturbed emotions can adversely affect the cortico-hypothalamo-hypophyseal relationships, thereby producing pathological endocrine changes. The exact nature of the mechanism by which these changes are produced is still the subject of some debate, since so few nerve fibers enter the anterior lobe of the pituitary gland from the hypothalamus. A neurohumoral theory, however, has been postulated to explain the manner in which the hypothalamus exercises control over the pituitary

TABLE I. PSYCHODYNAMICS OF FUNCTIONAL PELVIC DISORDERS

Emotionally Immature Dependent Personality + Situational Stresses
1. Sibling rivalry
2. Competitive, independent striving
3. Social, economic and occupational hazards
4. Marital incompatibilities, etc.

↓

Unresolved Conflict and Anxiety

↓

Chronic Increased Autonomic Tension

↙ ↘

Local effects
(1) muscular
(a) bladder
(b) colon
(c) uterus, etc.
(2) vascular
(a) pelvic congestion, etc.

Systemic effects
(1) pathologic impulses through the hypothalamic tracts to
(a) pituitary gland
(b) adrenal glands
(c) ovaries

↘ ↙

Psychosomatic Disorders

(1) dyspareunia, vaginismus, and frigidity
(2) dysmenorrhea, amenorrhea, and menometrorrhagia
(3) obesity, sterility, pseudocyesis, and abortion
(4) constipation, diarrhea, urinary incontinence and retention
(5) hyperemesis gravidarum, toxemias of pregnancy, and pathological labor
(6) pelvic pain, backache, menopausal syndrome, etc.

↓

Secondary Gains

(1) increased sympathy and attention by family and physician
(2) gratification of other dependent needs

↓

Partial Reduction of Anxiety and Tension

↓

Unstable Emotional Equilibrium

secretory activity, and, while it lacks full documentation, few investigators would deny that the emotions play a profound role in influencing pituitary hormonal activity, and through it also exercise far-reaching effects on other hormonal and metabolic processes.

As yet we are unprepared to answer why one patient will develop such a disturbance, whereas another patient under similar stresses does not. Some of the factors which alter the individual's vulnerability are the degree of emotional immaturity, and the quality, intensity, and *chronicity* of the noxious stresses as well as the setting in which these are handled. The amount of emotional strain that can be comfortably tolerated not only differs widely among individuals, but varies greatly in the same woman during the span of her active life. It is of no little importance, therefore, to inquire into the relative adjustment of the patient's earlier background in an attempt to assess her resourcefulness in dealing with trying circumstances. This principle is of therapeutic as well as diagnostic value since, in despondent moments, it is of considerable help to encourage free recall of the more satisfactory periods of the patient's life.

While we recognize the difficulty of setting down any fully accepted schematic representation, a chart has been formulated to demonstrate the mechanisms generally involved in the production of the psychosomatic obstetrical and gynecological disorders (Table I). Obviously this chart cannot illustrate every significant factor in the equation, and it has been necessary to omit the important aspect of early traumatic experiences which sensitize certain specific organs to the later development of functional disorders. Likewise the role of hate, guilt, and fear in the production of conflict and tension is too broad to be included without further clarification.

In order to clarify our approach for the reader, several cases have been briefly abstracted to illustrate a few of the problems encountered, and the manner in which they were managed.

Functional Sterility and Uterine Inertia

Mrs. A. C., a 29-year-old white woman, was referred because of relative sterility of six months' duration. A previous pregnancy three years earlier had resulted in a spastic child following a normal vaginal delivery, and contraception had been employed for the following 2½ years. During the initial interview considerable hostility was expressed toward the original obstetrician, the pediatrician, and ultimately toward her husband with whom some residual sexual incompatibility yet existed. Her chief fear was that another damaged child would result from a subsequent pregnancy.

Physical examination revealed no gross pathology and it was decided to simply offer supportive reassurance to the patient. After the third interview she missed her menstrual period and was found to be pregnant. The pregnancy continued uneventfully until the last month when evidence of serious anxiety appeared in the form of insomnia, tension, and mild depression.

Though the patient was obviously disturbed on her admission to the hospital, she resisted any probing for the cause. Labor was of a desultory nature and after twenty hours no progress had been made. The patient demanded in desperation that something be done to activate her labor, but before resorting to uterine stimulation by the intravenous pitocin drip technique, it was decided to attempt a narcoanalytic interview. Accordingly, 100 mg. Demerol and 1/150 gr. Scopolamine were given intravenously over a period of fifteen minutes with startling results.

Within five minutes she was drowsy and relaxed and ventilated freely her concern over the fate of this baby. Amidst tears she confessed extraordinary guilt dating to a criminal abortion which was kept from both her parents and husband with difficulty. She believed that the spastic child had been retribution for her sin in destroying the first

pregnancy and pitied her husband for having to share this punishment. For increasing her guilt, however, she also despised him and remarked, "It is a relief to get this load off my chest."

Simultaneous with these emotional outbursts extremely active uterine contractions were initiated. Within 15 minutes she was sound asleep and in 1 hour and 35 minutes she spontaneously delivered a 7 pound, 4 ounce girl in excellent condition.

There are many lessons to be learned from this case report to which an entire paper could easily be devoted. Certainly it emphasizes the importance of subconscious repressed emotions and their influence on the function and dysfunction of the autonomic nervous system. It indicates further the need for the advocates of natural childbirth to recognize that fear is not necessarily related to labor pains alone. Many expectant mothers are far more concerned with deeper problems which are not resolved by the superficial approach of their currently popular programs.

Frigidity and Menorrhagia

Mrs. M. H., a 24-year-old white woman complaining of "female trouble," was referred to the gynecological clinic from the medical department with a diagnosis of chronic pelvic inflammatory disease. Typical of our patients with multiple somatic complaints, she listed her symptoms in the following order: pelvic cramps, backache, and vaginal discharge—but associated with them on further inquiry were secondary headaches, insomnia, loss of appetite, dysuria, nocturia, and alternate diarrhea and constipation.

She was married at the age of 14, had two children and was divorced at the age of 19. For the next few years her menses gradually increased in duration and activity, lasting at times two full weeks. A curettement was required one time because of the excessive bleeding.

Following her second marriage she got along fairly well until after the painful delivery of her third child. Her husband became irritable with her and the children because of her reluctance to engage in sexual intercourse. In part she explained this upon her fear of becoming pregnant again. A careful examination in our clinic revealed no pelvic inflammatory disease, but rather a tense, anxious young woman.

To her great relief a contraceptive diaphragm was fitted at the Planned Parenthood Clinic. With the help of a mild sedative her irritability and insomnia improved, but not her libido. Consequently she was started upon testosterone propionate 25 mg. intramuscularly three times a week and almost immediately noted a change in her sexual attitudes, upon which her husband also commented favorably. At the last interview (five weeks following the initial visit) the patient stated, "I think, Doctor, you have performed a miracle for me. My husband is more satisfied with our relationship and I no longer pick on him or the children. Since my nerves are more settled, my symptoms have vanished."

Through the combined use of testosterone and psychotherapy our results in treating frigidity have been exceptionally gratifying. The rational for using testosterone is still highly speculative, and more detailed study is required before intelligent conclusions can be drawn. We have reason to believe that the occasional failure reported from its use may be due to the improper selection of patients, especially those whom we classify as cases of *pseudofrigidity*. After unsuccessfully treating several supposedly frigid women with testosterone, we learned, to our chagrin in subsequent interviews, that the frigidity was expressed only toward their husbands, while they were simultaneously maintaining satisfactory sexual relationships with other men. Because of the very real danger of masculinization from overdosage, the profession is seriously cautioned against the indiscriminate employment of this hormone. If the monthly dosage is maintained under 300 mg., such complications are infrequent, though not entirely absent. Acne and hoarseness often herald the more serious changes and

these can be eliminated by ceasing medication for one to two weeks. If no response occurs with this dosage, the physician should carefully review the case before continuing therapy.

Pelvic Pain and Pseudocyesis

Miss M. F.,* a 29-year-old white woman, was referred because of diffuse pelvic pain and premenstrual tension. Although she was unmarried, pelvic examination was accomplished with ease and revealed no pathology whatever. Following the examination, the patient accepted with some doubt the reassurance that no pelvic pathology existed and asked whether one could be absolutely sure that there was nothing wrong. When asked to explain the reason for her doubt, she stated merely that she had recently been told by a young man with whom she had intercourse that she was "built peculiarly inside" and that she should never have intercourse again. She refused at this visit to go into further detail.

Upon her own request, the patient was seen again two weeks later, at which time the entire picture had changed. At this time she was confused and actively hallucinated during the entire interview. She spoke of being under the "hypnotic spell of a ventriloquist," and elaborated by saying that there could be no other explanation for the voices and conversation she would hear when alone or in a group because "if someone isn't throwing his voice from a distance, I would have to be crazy, and I am sure I am not." She believed a spell had been cast upon her during the wedding ceremony of her dearest girl friend and that others present had been similarly affected. The hallucinatory material was incoherent and bizarre, involving some process by which people could be turned into "zombies" by having fellatio performed upon them without their knowledge. Since the patient appeaerd neither dangerous to herself nor to others, she was instructed to return the following week. She began this interview by speaking of her job and talked rationally for several minutes until she lapsed into details of her hallucinatory experiences.

After the fourth interview, the patient dropped all references to the previous psychotic ventilations and proceeded to discuss actively her personal problems. It was noted that she had been raised with a brother 12 years her senior in a poor environment by parents who rejected her and offered no emotional security. Though she was attracted, during the past five years, to several young men, she admitted that the relationships had ended rather quickly because she was interested primarily in marriage to escape her home situation, and the boys, on the other hand, were interested primarily in sex. About six months prior to the present illness, she became attracted to a supervisor in her office whom she dated on several occasions, on one of which she was persuaded to engage in sexual intercourse, believing it would lead to marriage. She had intercourse with him four times, but only during the last episode achieved an orgasm which, she says, "paralyzed her and left her unconscious for 15 to 20 minutes." It was following this relationship that the man cautioned her never to have intercourse again, probably because the experience had frightened him as much as it had her. From that night on he avoided the patient's company. In the subsequent two months she developed a typical pseudocyesis with amenorrhea and enlargement of the breasts and abdomen; and not until two rabbit tests had been performed could she be convinced by her physician that she was not pregnant. With the reappearance of the menses, however, her present illness began.

By the twelfth interview the patient was prepared to accept partial insight into her problem. She was able to recognize without panic that her early behavior had been quite psychotic and represented, in part, an attempt to solve the conflict resulting from having been rejected. No attempt was made to interpret for her the significance of her psychotic fantasies, and it is interesting moreover to report that during all of this period the patient lost no time from her work and made no further reference to any pelvic complaint,

*From the author's private practice.

It has now been eight months since she agreed to discontinue treatment, but she has called at intervals of two to four weeks to report on her condition. Thus far it has remained good.

It is not our policy ordinarily to follow a psychotic patient in the manner described, but since this patient had originally sought help from the gynecologist, with whom she quickly established an excellent relationship, the therapy was attempted as an experiment. We were gratified with the final results chiefly for the patient's sake, but it must be admitted that the experience gained from this fascinating case more than justified the expenditure of the time required.

Comment

The multitude of therapies currently employed and recommended in the management of the disorders under discussion have obviously but *one* denominator in common—*the therapist.* Various investigators have reported with equal enthusiasm excellent results in the treatment of dysmenorrhea and amenorrhea, for example, through the use of gonadotropic hormones, estrogen, testosterone, progesterone, stilbestrol, thyroid, Adrenalin, Benzedrine, belladonna, Benadryl, phenobarbital, intrauterine pessaries, dilatation and curettage, ovarian resection, presacral neurectomy, x-ray, diathermy, exercises, rest, relaxation, and psychotherapy. Certainly it must have occurred to others as it has to us that, in critically analyzing any of these reports, the relation of the specific therapist to the particular patient is of the most fundamental importance—perhaps even more important than the particular therapy employed. Any author who fails to correct for this significant factor permits "statistical blind spots" to invalidate his conclusions.

There are some who may challenge our work on the basis that it lacks adequate scientific documentation. If it is meant that one cannot establish positive proof of the psychogenic influence on the endocrine system without repeated hormone level determinations during the therapeutic program, the authors heartily agree. No one would desire more than we, the laboratory facilities to do such studies routinely during our investigations, but such facilities are costly and not within the budget of most clinics. Moreover, other investigators like Rakoff[20] and his co-workers are currently engaged in work along these lines.

On the other hand, honestly recorded clinical observations are also scientifically valid and cannot be denied. We sincerely believe that there is not only room, but considerable need, for further documentation in both the clinical and the experimental spheres of investigation. Rakoff has, for example, shown that despite the knowledge gained in hormonal assays, these are often of little assistance in therapy by the various endocrine preparations and he concludes that "The patients most resistant to psychotherapy are also often the most resistant to hormonal and other methods of treatment." From clinical observations we have known this for a long time and therefore feel justified in recommending the program which has been described in the body of this paper as a sensible clinical approach to the psychosomatic pelvic disorders.

No attempt has been made in this preliminary report to present a large body of statistical data since the project is too new for accurate statistics and we are not yet convinced that they have much to offer in the clinical management of these problems. This clinic program is still in the process of technical formulation, and no doubt many procedures will have to be added or modified to cope with its expanding facilities. Our ultimate goal is to have someday a well-integrated clinical and experimental research department staffed by a gynecologist, obstetrician, endocrinologist, psychiatrist, psychologist, social worker, and laboratory technician. In the interim, a service is being offered to patients which fills a long-neglected area in the clinic setting.

Considerable emphasis is being placed on the teaching aspect of the program by case supervision of the resident house staff and informal seminar discussions. The house staff recognize and welcome this addition to their diagnostic and therapeutic armamentarium, but at the same time they are being taught the value of caution, the danger of overzealousness, and the need for an intelligent, well-balanced approach—neither too psychic nor too somatic. Everyone connected with the project is convinced that the training being offered to the house staff will materially contribute to their preparedness for dealing intelligently with similar problems in practice. Above all, it has been constantly stressed that these concepts are intended as a supplement to and not as a substitute for that material already available in the many standard obstetrical and gynecological reference texts.

Summary

The incidence of obstetrical and gynecological psychosomatic illness is probably in excess of any estimate thus far published, since it appears likely that nearly every woman will at some time develop such a disorder due to the complex integration of her emotions and sexuality. Unfortunately, more is involved than merely a medical problem. Deeply significant are the broad sociological implications, for underlying countless divorces and broken homes are the many unrecognized, neglected, or mishandled sexual disorders. Few mothers with a serious psychosexual disturbance are capable of providing the proper environment for either bearing or rearing emotionally healthy children.

Since the numerical shortage of psychiatric personnel makes it wholly impractical to refer all such women for psychotherapy, the obvious solution to the current problem is to train the practitioner in the principles of the psychosomatic approach. Even in this limited capacity, each physician can make a lasting contribution toward raising the standard of available medical service. By establishing liaison with a qualified psychiatrist for consultation purposes, a greater degree of definitive care can be afforded those women who require it.

Without entering into highly technical psychiatric language, an attempt has been made to explain the general dynamics of these problems, but from the evidence now available, it is difficult to speak in terms of psychosomatic specificity to the same degree as is sometimes done in the cardiovascular or gastrointestinal disorders. We believe that the hypothalamus acts as a relay station through which disturbed emotions may find expression in pathologic endocrine physiology. By means of a modified analytic talking-out technique in conjunction with other accepted therapeutic agents, these pathologic mechanisms can frequently be altered sufficiently to restore normal pelvic and hormonal physiology. Our ultimate aim, naturally, is to reintegrate the patient as rapidly as possible back to her family or occupation, with a better capacity for adaptation. Toward this end, treatment is not unduly prolonged, in an effort to discourage the development of too deep transference dependent relationships.

Conclusions

1. Not every physician is obliged to undertake prolonged psychotherapy in the management of these disorders, but it is incumbent upon him to become

sufficiently acquainted with the problem to be able to recognize the psychogenic aspects of the illness and to avoid irrational therapy.

2. The experience necessary to participate successfully in this program will result not only from the interest and equipment which the physician brings with him, but also from the frequency with which he employs them in the therapeutic setting. That knowledge which is derived from direct observation of the patient cannot be substituted by reading from any source.

3. Brief therapy by the gynecologist and obstetrician is justified on the basis of our clinical results, and, by reducing the psychiatrist's burden, more time is available to him for those patients requiring deeper therapy.

4. Finally, it is important for the physician to be mindful of his limitations and to recognize that qualified psychotherapists cannot be produced by an improvised assembly-line technique on the assumption that the more there are the better it is for everyone.

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Medical Arts Building

ATTEMPTS AT DESENSITIZATION OF WOMEN IMMUNIZED BY THE RH FACTOR

I. The Use of Ethylene Disulfonate

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HEMOLYTIC disease due to maternal isoimmunization by the Rh factor occurs in about 0.66 per cent of newborn infants. Since the advent of transfusion therapy, and especially with the use of exchange transfusion employing female donors, more than 90 per cent of infants born alive with hemolytic disease are saved.[1] Nevertheless, the tragic problem of helping heavily sensitized women who give birth repeatedly to stillborn and hydropic infants has not been solved. Moreover, it is a question whether exchange transfusion either modifies or prevents kernicterus, the disastrous brain damage which occurs in from 10 to 15 per cent of infants with hemolytic disease of the newborn.

Personal experience with a large number of cases in our clinic in the past four years has served to emphasize the calamitous nature of the Rh problem for some women. Many cases were discovered during routine blood grouping and Rh testing in pregnancy; others were referred for study as problem cases. No over-all statistical validity can be claimed for this somewhat selected material, but it is worth noting that in this series to date there have been 218 cases of hemolytic disease of the newborn. Of this group there were 97 fetal deaths; these cases consisted of 31 stillborn, 22 hydrops fetalis, 23 kernicterus, 6 infants with severe hemolytic disease, and 15 cases in which further autopsy studies are being carried out to determine the exact cause of death (see Table I).

TABLE I. ANALYSIS OF 218 CASES OF HEMOLYTIC DISEASE OF THE NEWBORN
(December, 1945, to December, 1949)

Surviving Infants.—	
Mild	38
Moderately severe	48
Severe	29
Kernicterus	6
Total	121
Dead Infants.—	
Hydrops fetalis*	22
Stillborn	31
Kernicterus	23
Severe hemolytic disease	6
Cause of death to be determined†	15
Total	97

*Seven stillborn.
†Eight died during exchange transfusion.

It is obvious that no form of postnatal treatment will save infants fatally afflicted in utero and the importance of developing a method of prevention of hemolytic disease in the newborn seems self-evident. To date, a number of methods for attempting prevention of hemolytic disease of the newborn have been advocated, and no doubt others will be forthcoming. Each requires critical analysis based on a sufficient number of specifically treated cases if statistically valid conclusions are to be obtained. This is especially important because of the well-known variability of erythroblastosis fetalis, not only from patient to patient but from one pregnancy to another in the same patient.

Several years ago Wiener and Sonn[2] proposed the use of typhoid and pertussis vaccines during pregnancy in the hope that these bacterial antigens would "compete" with Rh antigens for the maternal immune mechanism. Wiener reported one case in which he felt this procedure had prevented hemolytic disease, but the evidence presented was unconvincing. Experience with a series of women *treated during pregnancy* with pertussis vaccine and agglutinogen has shown that this approach is not only useless but may be harmful (data to be published).

In 1947 Kariher[3] reported on a successful use of ethylene disulfonate for the "prevention" of Rh sensitization in pregnancy. That the infinitesimal amounts of this drug could prevent immunization seemed unlikely, but as part of a program to investigate methods of prevention of isoimmunization in pregnancy, ethylene disulfonate was administered to a series of women and the results are reported in this paper.

Since this work was carried out, the supposed chemical isolation of Rh hapten has been claimed by Carter[4] and subsequently the successful use of this so-called hapten for the prevention of hemolytic disease of the newborn has been reported.[5] This "hapten" has been expensive to produce and difficult to obtain, but a series of 10 women receiving this material are under investigation and the results of "hapten" therapy will be reported in another paper.

Experience with various attempts at prevention of hemolytic disease of the newborn has demonstrated many of the pitfalls and difficulties involved in evaluation of any method employed. In the selection of cases, while it is true that the history of hemolytic disease in a prior pregnancy is extremely important, it has been repeatedly noted that severe hemolytic disease has been followed by a milder form of the disorder or a normal Rh-positive infant. This is true also of kernicterus and in this series six women have given birth to infants who died of kernicterus, yet in the next pregnancy infants with hemolytic disease have survived without evidence of brain damage. If the prior pregnancy has resulted in a stillbirth or an infant with hydrops fetalis and there is strong hyperimmune antibody present in the mother's serum, survival of the infant is very unlikely. Nevertheless, even under these circumstances a living infant may be delivered without specific treatment and may survive.

Much has been written concerning the nature, activity, and behavior of Rh antibody during pregnancy.[6] It is not the purpose of this study to discuss the significance of antibody titers or the technical problems involved. However, in following many of these women through pregnancy, the variability of antibody levels has been striking. Frequently there has been a marked discrepancy

TABLE II. DATA ON CASES TREATED WITH ETHYLENE DISULFONATE AND WITH DISTILLED WATER

CASE NO.	NAME	AGE	GRAVIDITY	E. D. C.	DATE DELIVERED	ETHYLENE DISULFONATE		TOTAL AMOUNT (C.C.)	OUTCOME
						BEGAN	FINISHED		
1	F. K.	33	iv	5/ 5/48	4/ 3/48	11/11/47	3/29/48	39	Hydrops—dead
2	S. C.	30	iv	4/30/48	4/26/48	1/ 6/48	4/ 5/48	18	Severe hemolytic disease—died
3	M. C.	28	iv	5/22/48	5/ 2/48	10/ 4/47	4/20/48	52	Stillborn
4	H. B.	36	v	2/23/48	11/27/47	10/16/47	12/18/47	10	Stillborn*
5	M. B.	26	iv	2/12/48	1/22/48	10/ 8/47	1/22/48	24	Normal infant†
6	R. M.	34	viii	7/28/48	7/ 7/48	3/15/48	6/18/48	18	Hydrops—died
7	E. C.	31	iv	1/29/48	1/ 9/48	10/ 9/47	1/ 2/48	26	Hemolytic disease—lived
8	R. P.	31	iv	7/15/48	6/11/48	1/28/48	6/ 8/48	40	Hydrops—died
9	M. L.	27	v	5/ 9/48	2/20/48	10/10/47	2/ 6/48	34	Died on 5th day*
10	O. L.	40	iv	10/ 8/48	9/23/48	4/12/48	9/20/48	46	Hydrops—died
11	N. K.	37	iv	7/20/48	7/11/48	4/27/48	7/ 6/48	20	Normal infant†
12	A. B.	35	v	10/30/48	10/13/48	4/ 8/48	7/19/48	14	Normal infant†

*Distilled water.
†Rh negative infant.

between the concentration of antibody in the maternal serum and the extent of fetal damage, an observation which has been stressed by others.

In determining the usefulness of any method of prevention of hemolytic disease in the newborn, the necessity of careful selection of cases for therapeutic trial has become increasingly obvious; otherwise equivocal and misleading findings will result. An ideal series of cases should include a significant number of women with the following qualifications:

1. Homozygous husbands (with anti-c).
2. Hyperimmune antibody present in maternal serum.
3. History of loss of at least the prior pregnancy (stillbirth or hydrops fetalis) due to hemolytic disease.
4. Therapy started early, preferably in the first trimester.

While these are strict criteria, experience, as demonstrated in the following reports, has shown that the variability of the outcome under other circumstances makes accurate evaluation of preventive measures very difficult.

The present paper is concerned with observations on the use of ethylene disulfonate in a group of heavily sensitized women during pregnancy.

Methods and Materials

The ethylene disulfonate* was furnished by the manufacturer and with it were supplied individual dry sterile syringes and needles. The technique of administration advocated by the maker was faithfully carried out: no antiseptic was used on the skin and all injections were given deeply into the deltoid muscle. As noted by Kariher,[3] no untoward effects were encountered from the drug. The injections were quite painful and fibrillary twitching of the muscle occurred in nearly all cases. A dosage schedule of 2 c.c. a week was attempted, but this was not possible in all cases. The injections were started as early as possible in pregnancy and antibody studies were carried out every two weeks using bovine albumin as the diluent.[7] Rh_1 (CDe) cells fresh from a single donor were used throughout to insure as uniform results in titration of antibody as possible.

Twelve women sensitized to the Rh factor were selected for this study. All but three women had lost infants due to hemolytic disease and all but one had a prior history of an erythroblastic infant. Of this group, two patients were given injections of distilled water, the other ten were given ethylene disulfonate. (See Table II.)

Report of Cases and Experimental Results

CASE 1.—Mrs. F. K., 33 years old, gravida iv, estimated date of confinement May 5, 1948. The history of her prior pregnancies was as follows: the first child was a normal full-term infant; the second was full-term but became icteric and died on the fourteenth day; the third pregnancy also resulted in a full-term icteric infant and this child died on the tenth day.

During the present pregnancy the patient was first seen on Nov. 1, 1947, and was found to have strong hyperimmune anti-Rh antibody in her serum. The patient was started on ethylene disulfonate on Nov. 11, 1947, and she was given a total of 39 c.c. during her pregnancy. Although the antibody titer fell (Fig. 1) and in spite of early induction, the infant was edematous and expired within ten minutes of birth.

*The ethylene disulfonate used in this study was Allergosil brand, kindly furnished by the Spicer-Gerhart Company.

CASE 2.—Mrs. S. C., 30 years old, gravida iv, estimated date of confinement April 30, 1948. This patient's first pregnancy resulted in a full-term normal infant. The second infant was also normal, but following delivery the patient had a severe postpartum hemorrhage. She was given several transfusions; *one donor was the patient's husband.* The third pregnancy resulted in an eighth-month stillbirth.

During the present pregnancy the patient was first seen on Dec. 9, 1947, and was found to have a large amount of hyperimmune antibody. She was started on ethylene disulfonate on Jan. 8, 1948, but was irregular in coming for her injections and received only a total of 18 c.c. No notable effect was observed on the antibody titer (Fig. 1) and the infant was delivered three weeks before term by cesarean section. At birth the infant was obviously icteric and anemic. An exchange transfusion was immediately carried out using the method of Diamond,[6] but the infant expired twenty-four hours after birth. At autopsy, findings were consistent with severe hemolytic disease and the brain showed typical lesions of kernicterus.

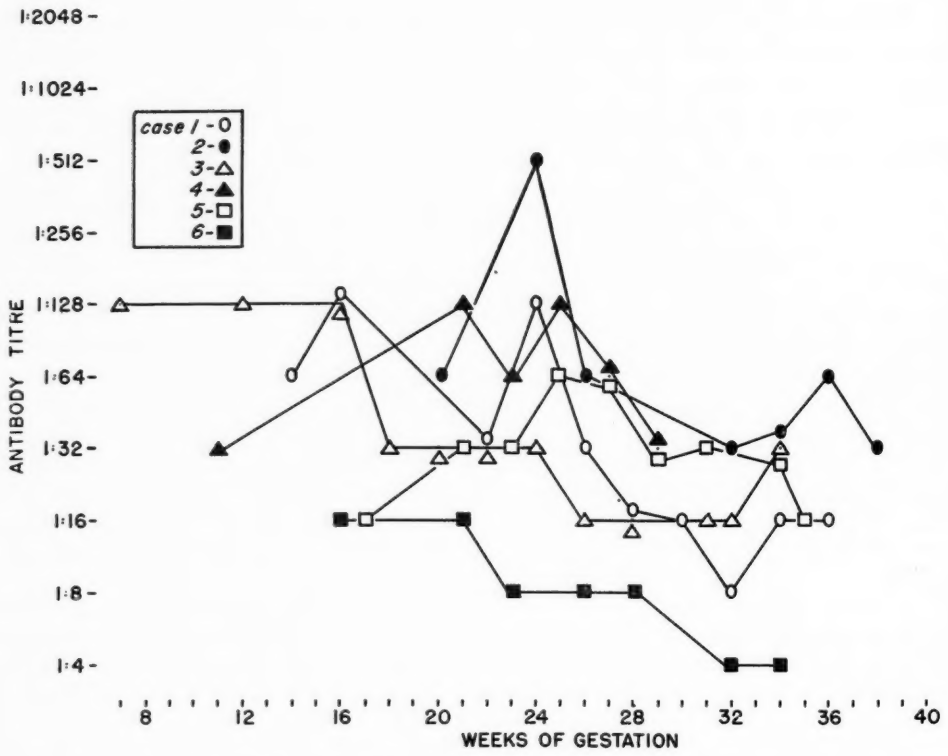

Fig. 1.—Behavior of antibody following administration of ethylene disulfonate and distilled water.

CASE 3.—Mrs. M. C., 28 years old, gravida iv, estimated date of confinement May 22, 1948. The first and second pregnancies resulted in full-term normal living children. The third pregnancy terminated spontaneously at seven months with stillborn twins, and a diagnosis of hemolytic disease was made at the time. The husband was Rh positive, probably homozygous.

In the present pregnancy the patient was first seen on Oct. 4, 1947, and was found to have a high titer of hyperimmune antibody in her serum. Injections were started early in pregnancy and a total of 52 c.c. of ethylene disulfonate was administered, but fetal movements ceased at 36 weeks and a stillborn macerated fetus was delivered several days later. Although the antibody titer dropped from its original high level, a considerable amount of antibody remained throughout pregnancy (Fig. 1) and the ethylene disulfonate had no influence on the outcome.

CASE 4.—Mrs. H. B., 36 years old, gravida ix, estimated date of confinement Feb. 23, 1948. This patient had five full-term normal pregnancies but her sixth pregnancy resulted in a sixth-month miscarriage and the seventh and eighth pregnancies terminated at eight months with stillborn infants. Very early in the present pregnancy, Aug. 9, 1947, the patient was found to have strong hyperimmune antibody. In October the antibody titer was higher and she was started on injections of distilled water intramuscularly. The patient had received only a total of 10 c.c. of distilled water before fetal movements ceased. As could be expected, this treatment had no effect on her titer (Fig. 1) and in December she delivered a macerated fetus.

CASE 5.—Mrs. M. B., 26 years old, gravida iv, estimated date of confinement Feb. 12, 1948. This patient had toxemia with her first pregnancy but was delivered of normal twins. The second pregnancy resulted in a six-month miscarriage. In her third pregnancy the patient was induced early and gave birth to an icteric infant with mild hemolytic disease which survived without transfusion.

Although the husband was probably heterozygous, during the present pregnancy the patient was found to have antibody and she was started on ethylene disulfonate on Oct. 8, 1947. A total of 24 c.c. of the drug was given but no appreciable effect was noted on the antibody level. (Fig. 1) She was induced at 38 weeks and delivered spontaneously of a normal Rh-negative infant.

The antibody was carried over from the prior pregnancies but the titer rose as if immunization was proceeding, the antibody behavior simulated that noted with Rh-positive infants, and of course it was not possible to decide prenatally whether the fetus would be Rh positive or Rh negative.

CASE 6.—Mrs. R. M., aged 34 years, gravida viii, estimated date of confinement July 28, 1948. This patient had a particularly bad obstetrical history. Her first two pregnancies were full-term normal infants. The third infant was full term but jaundiced and died soon after birth. The fourth infant was full term, stillborn. The fifth, sixth, and seventh pregnancies resulted in miscarriages at the third and fourth months. Following two of these miscarriages the patient was given a total of four transfusions. At the time no tests were carried out for the Rh factor and it was quite certain the patient received Rh-positive blood.

In the present pregnancy the patient was first seen on Feb. 28, 1948, and at that time she had a titer of 1:16 in albumin. Ethylene disulfonate was started March 15, 1948, but the patient received injections rather irregularly as she was edematous and felt poorly throughout her pregnancy. On July 7, 1948, a cesarean section was performed and a living but very edematous and anemic infant was delivered. In spite of immediate exchange transfusion and the administration of salt-poor human albumin,* the child expired within an hour after birth.

This case is a good example of the fact that high titers of antibody need not be present with severe hemolytic disease (Fig. 1.). It is also another illustration of the tragedy of the heavily sensitized woman with a homozygous husband. Unfortunately, only 18 c.c. of ethylene disulfonate were given to this patient, but no apparent beneficial effect could be attributed to this therapy.

CASE 7.—Mrs. E. C., aged 31 years, gravida iv, estimated date of confinement Jan. 29, 1948. The patient's first pregnancy in 1942 resulted in normal twins, but due to a severe postpartum hemorrhage she was given 3 pints of blood. At that time no precautions concerning the Rh factor were taken, and the patient had a severe reaction following one transfusion. The second pregnancy resulted in a full-term icteric infant that died in spite of blood transfusions. The third pregnancy resulted in a full-term normal Rh-negative infant.

*The human serum albumin used in this case was provided without charge by the American National Red Cross.

The first antibody study in the present pregnancy was carried out on Sept. 29, 1947, and the titer in albumin was 1:32. A month later the titer was 1:128 and ethylene disulfonate was started at this time. The patient received a total of 26 c.c. of ethylene disulfonate and was induced and delivered on Jan. 9, 1948. The infant appeared normal at birth and weak antibody (in albumin) was discovered in the cord blood. However, within the first 18 hours after birth the infant rapidly developed deep icterus. An exchange transfusion was carried out and the infant made a good recovery. Ethylene disulfonate could not be said to have influenced the outcome in this case. High titer antibody persisted throughout pregnancy (Fig. 2) and exchange transfusion may have played an important role in saving this infant.

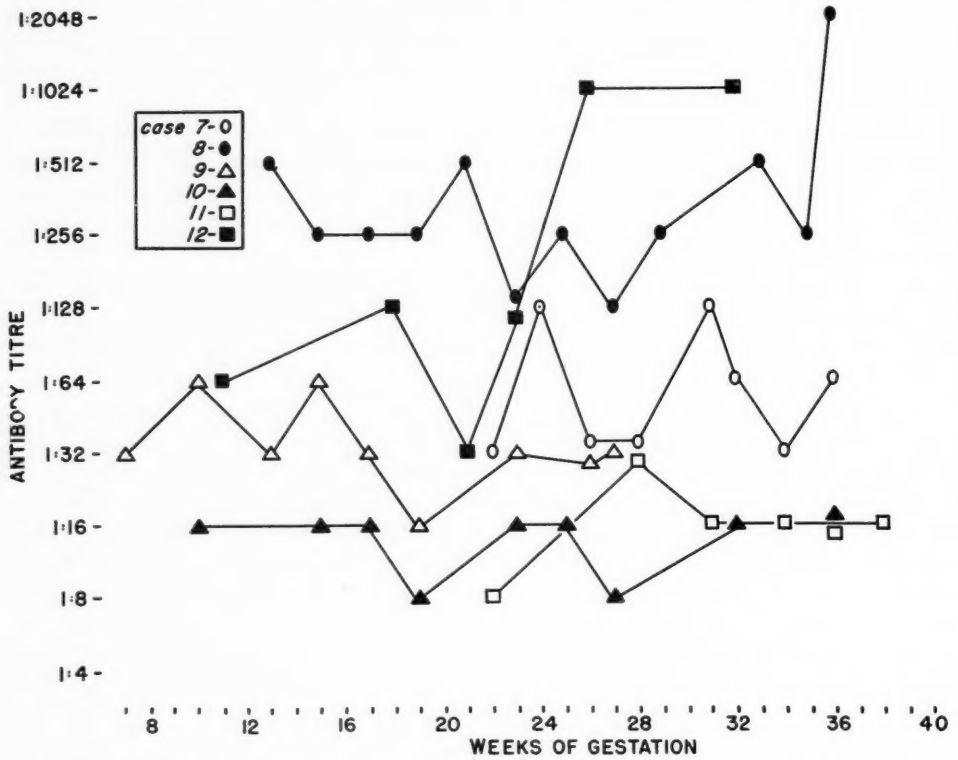

Fig. 2.—Behavior of antibody following administration of ethylene disulfonate and distilled water.

CASE 8.—Mrs. R. P., aged 31 years, gravida iv, estimated date of confinement July 15, 1948. This patient had a probably homozygous husband and her past obstetrical history was ominous. The first pregnancy ended in a full-term infant normally delivered. The second resulted in an icteric infant who expired six hours after birth. The third pregnancy terminated in a stillborn infant.

In the present pregnancy the patient was first seen on Jan. 15, 1948, and she had a titer of 1:512 in albumin. Ethylene disulfonate was started on Jan. 28, 1948, and she received weekly injections throughout the remainder of pregnancy. She was delivered on June 11, 1948, by cesarean section of an edematous anemic infant who died in ten minutes.

CASE 9.—Mrs. M. L., aged 27 years, gravida v, estimated date of confinement May 7, 1948. This patient had four normal full-term deliveries without evidence of hemolytic disease. However, early in the present pregnancy, on Sept. 20, 1947, the patient had a titer of 1:32 in albumin. As a control on the administration of ethylene disulfonate the patient was given weekly injections of 2 c.c. distilled water intramuscularly. On Feb. 20,

1948, the patient had a nontoxic separation of the placenta. She delivered spontaneously a 6½-month premature fetus which expired on the fifth day. Autopsy showed evidence of prematurity. As shown in Fig. 2, the distilled water did not influence the antibody titer. It was impossible to state what role therapy had in this case.

CASE 10.—Mrs. O. L., aged 40 years, gravida iv, estimated date of confinement Oct. 8, 1948. This patient's husband was probably homozygous. The first pregnancy resulted in delivery of an eight-month fetus which expired in one hour. Cause of death was undetermined. The second pregnancy resulted in a full-term normal infant and the third in a full-term icteric infant who survived following blood transfusions.

When first seen in the present pregnancy on March 13, 1948, she had a titer of 1:16 in albumin. Ethylene disulfonate was started on April 12, 1948, and continued throughout pregnancy until Sept. 14, 1948. On Sept. 21, 1948, fetal movements ceased and the patient delivered spontaneously of a dead hydrops infant on the following day. This patient received a large amount of ethylene disulfonate (46 c.c.) but there was no beneficial effect. The antibody concentration did not rise but remained constant throughout pregnancy. (Fig. 2.) This case furnishes additional evidence of the difficulty in evaluating antibody levels in regard to fetal damage.

CASE 11.—Mrs. N. K., aged 37 years, gravida iv, estimated date of confinement July 1948. This patient's husband was probably homozygous. The first pregnancy resulted in the birth of an infant with moderately severe hemolytic disease. This infant recovered after several small transfusions.

This patient was first seen in the present pregnancy on March 12, 1948. The antibody titer was 1:8 in albumin. On April 27, 1948, the titer had risen to 1:32 and she was started on ethylene disulfonate. The patient was not very faithful in coming in for her injections and she received a total of only 20 c.c. of ethylene disulfonate. The patient was induced and delivered on July 11, 1948. The infant was Rh negative and normal in every respect. As shown in Fig. 2, the antibody titers remained fairly constant throughout the late part of pregnancy.

CASE 12.—Mrs. A. B., aged 35 years, gravida iv, estimated date of confinement Oct. 30, 1948. This patient's husband was found to be probably heterozygous, but due to the unusual history it was decided to include her in this study. The first pregnancy resulted in a living normal infant. This child was found to be Rh negative. On the second pregnancy, in 1945, the patient gave birth to a very icteric full-term infant who expired soon after birth. Autopsy demonstrated a classical picture of hemolytic disease of the newborn. The patient became pregnant for the third time in 1946 and she was followed throughout pregnancy with frequent antibody determinations. During her third pregnancy the patient was given a course of injections of pertussis antigen in a study on the effect of competition of antigens. No beneficial effects were noted, Rh antibody production continued unabated, the patient was induced and she again gave birth to a normal Rh-negative infant.

In the present pregnancy she maintained a very high antibody titer but reported very sporadically for ethylene disulfonate injections. A total of only 14 c.c. was injected and no effect was noted on the antibody titer. (Fig. 2.) She again delivered a normal Rh-negative baby. This case epitomizes some of the difficulties in the problem of Rh isoimmunization. Whether the rise in the antibody titer during her pregnancies was due to an anamnestic (or "recall") reaction in a very easily sensitized individual is a matter of speculation. In any event the small amount of ethylene disulfonate administered to this patient had no effect on the antibody levels.

Comment

In an analysis of the cases treated in this series there were four surviving infants, and of this group three were Rh negative (Cases 5, 11, and 12). The high titer and behavior of the antibody in Case 12 (Fig. 2) were especially interesting in view of the fact that the infant was Rh negative. In all three cases

relatively small amounts of ethylene disulfonate were given and in no instance was there any influence on the antibody level. (Figs. 1 and 2.) The only surviving Rh-positive infant (Case 7) had moderately severe hemolytic disease. Induction at 38 weeks now believed to be of doubtful value and exchange transfusion resulted in a living infant. This mother received 26 c.c. of ethylene disulfonate in all, but no effect on the antibody titers could be demonstrated (Fig. 2).

Of the remaining 8 cases, 2 mothers received distilled water instead of ethylene disulfonate. Kariher[3] states that the concentration of ethylene disulfonate is so extremely minute (amounting to 0.000000000002 mg. per each 2 c.c.) that distilled water might accomplish the same results. In one instance (Case 9) the mother received 34 c.c. of distilled water. No influence on the antibody titers was noted (Fig. 2) and the patient started in premature labor, delivering a very small feeble infant who expired on the fifth day. In this case the death was due to prematurity more than any other cause. One other patient (Case 4) was also given distilled water. However, this heavily sensitized mother received only 5 injections when fetal life ceased; subsequently she delivered a stillborn macerated fetus. No further use of distilled water has been attempted nor did further experiments seem warranted along this line.

Six Rh-positive infants were either born dead or died shortly after birth. As noted in Table II, one was stillborn (Case 3), 4 were cases of hydrops fetalis (Cases 1, 6, 8, and 10), and one infant with severe hemolytic disease expired in spite of exchange transfusion (Case 2). In this last infant the brain showed evidence of kernicterus at the unusually early age of 24 hours. Of this group of six infants, Cases 1, 3, 8, and 10 received early and large amounts of ethylene disulfonate (see Table II). In spite of this therapy, neither the antibody titers (Figs. 1 and 2) nor the outcome of the disorder was influenced in any beneficial degree.

A detailed criticism of Kariher's optimistic report seems unnecessary. The use of ethylene disulfonate lacks rationale as has been pointed out by a report of the Council on Pharmacy and Chemistry of the American Medical Association.[8] However, because of the widespread and uncritical acceptance of this form of therapy, it was considered advisable to attempt ethylene disulfonate injections in a series of cases. The experience here recorded indicates that this drug has no effect on isoimmunization by the Rh factor in pregnancy and does not prevent hemolytic disease of the newborn.

Summary and Conclusions

1. In this paper some of the difficulties in evaluating methods of prevention of hemolytic disease in the newborn have been pointed out. Suggestions as to criteria for the selection of clinical material for such studies have been outlined.

2. Observations are reported on a series of Rh-negative pregnant women, isoimmunized to the Rh factor, given ethylene disulfonate in ten cases and distilled water in two cases.

3. Of the 10 women treated with ethylene disulfonate, one infant survived following an exchange transfusion, three infants were Rh negative and escaped hemolytic disease, and six infants failed to survive.

4. Only two women were treated with distilled water instead of ethylene disulfonate and both infants died.

5. From the experience in this series of cases it is concluded that ethylene disulfonate exerts no influence on antibody production due to Rh isoimmunization, and that this drug does not prevent hemolytic disease of the newborn.

The author is grateful to Dr. L. K. Diamond and Dr. F. H. Allen for criticisms and suggestions in the preparation of this paper. The cooperation of the obstetrical staffs and blood bank personnel of a number of hospitals, especially St. Elizabeth's, Carney, St. Margaret's, Cambridge City Hospital, and Mount Auburn Hospital made these studies possible. Dr. Leo Smith carried out the exchange transfusions and was responsible for the pediatric management of most of the cases in this series.

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39 BAY STATE ROAD.

PREGNANDIOL EXCRETION AT THE TIME OF LABOR*†

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PREGNANDIOL is believed to be a urinary excretion product of the ovary and placenta,[1-4] and, on occasions, elaborated by the adrenal cortex.[5, 6] It is believed to be the end result of progesterone metabolism.[7-9]

Browne, Henry, and Venning,[10] in 1937, pointed out that the extraction of this substance, pregnandiol, during the first three months of pregnancy remained at approximately the same level as that found during the corpus luteum phase of the normal menstrual cycle; between 4 and 10 mg. in twenty-four hours. Thereafter the curve began to rise and by the one hundred fiftieth day had reached a level of 40 mg. By the seventh and eighth months, values as high as 60 to 100 mg. were obtained. The work of Browne and his co-workers seemed to imply, although no evidence was advanced to support the inference, that when labor began, large amounts of pregnandiol were still being excreted, amounts which did not fall appreciably until after delivery. (Fig. 1.)

In 1938, Wilson, Randall, and Osterberg[11] published their results on the extraction of pregnandiol from 47 gravid women. Although some patients characteristically passed large amounts of pregnandiol near term, others excreted comparatively small amounts. No reference was made to pregnandiol excretion immediately before and during labor. Later in the same year, Venning[12] drew attention to the excretion of pregnandiol at the two hundred eightieth day of pregnancy. Levels at this point ranged from 60 to 100 mg. Pregnandiol excretion immediately prior to and during labor was not stressed. Stover and Pratt[13] in 1939 doubted any marked drop in pregnandiol excretion just preceding the onset of labor. Bachman, Leekly, and Hirschmann,[14] on the other hand, in 1940, observed a fall in pregnandiol excretion prior to labor. It was their impression that labor appeared at a time when pregnandiol excretion ranged from 20 to 40 mg. daily. No curves were advanced for the period while labor was under way. Portes and co-workers[15] in 1941 also reported a considerable decline in pregnandiol excretion a few days before parturition.

Thompson, Musselman, and Geer[16] in 1941 reported on the excretion of pregnandiol by a woman who delivered prematurely. They were able to obtain a single uncontaminated specimen of urine totaling 215 c.c. prior to delivery in which were found 6 mg. of pregnandiol. Schneider[17] in 1942 studied pregnandiol excretion during the last seven months of pregnancy in two cases of sterility. One patient had a high of 110 mg. at the thirty-fifth week, the other a high of 50 mg. at the thirty-seventh week. Hamblen, et al.,[18] in a paper in 1942 commented on three patients who had histories of abortion but who progressed to term, one of whom excreted a high of 149 mg. several weeks before labor. In none was the urine analyzed immediately prior to and during labor.

*A portion of the thesis accepted by the Faculty of the University of Pennsylvania Graduate School of Medicine, Philadelphia, in partial fulfillment of the requirements for the Doctor of Medical Science degree (D.Sc., [Med.]) in Obstetrics and Gynecology.

†Presented before the Chicago Gynecological Society, Nov. 18, 1949.

In 1944, Guterman published the first of his important studies[19] dealing with a pregnandiol color reaction which he recommended for the diagnosis of pregnancy. The picture during late pregnancy and during labor did not receive comment. Jones, Delfs, and Stran[20] in the same year directed attention to a fall in pregnandiol excretion during the last ten days of pregnancy in three of six cases studied. In one instance, the daily pregnandiol dropped from 60 to 20 mg., in another from 150 to 30, and in the other from 100 to 35 mg. These investigators cited no data on how close to labor their studies were made and did not refer to the quantity, if any, of pregnandiol excreted while labor was in progress. In 1946, Lyon[21] reported on the excretion of pregnandiol as labor approached, in spontaneous labor at term, in spontaneous premature labor and spontaneous postmature labor. In all groups, he obtained low values of approximately 15 mg. daily prior to labor. He did not discuss the picture during labor. It was his opinion, however, that pregnandiol excretion at that period was negligible.

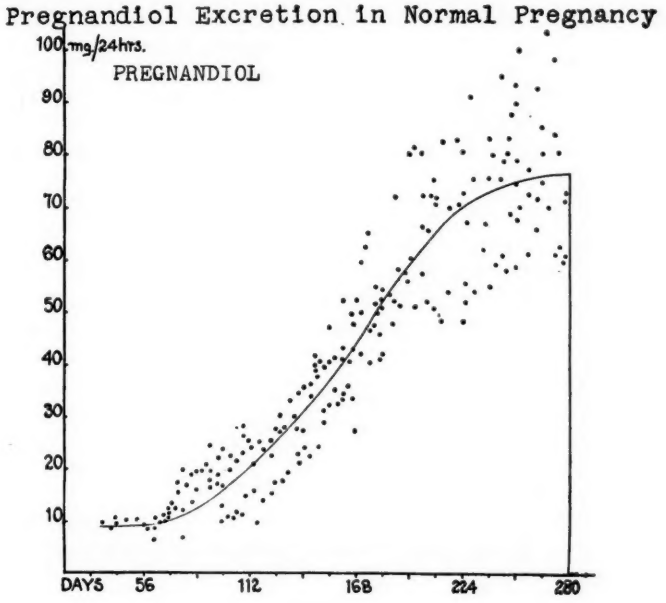

Fig. 1.

From the foregoing it can be seen that there has been a variety of opinions concerning pregnandiol excretion late in pregnancy and none on the picture with labor in progress. It was therefore concluded that further study immediately prior to and during full-term labor might clear up some of the uncertainty of pregnandiol excretion at a very critical period of gestation and possibly shed some light on the cause of labor as well. Accordingly, the present investigation was begun with those objectives in mind.

Technical Features*

Venning's gravimetric method for extraction was selected for use. This procedure consisted essentially of collecting a suitable amount of urine,

*The work was conducted in the Department of Physiology through the courtesy of Professor G. E. Wakerlin.

generally 500 to 1,000 c.c., which was extracted with four quantities of normal butyl alcohol totaling 375 c.c.; evaporation to dryness under reduced pressure of the combined butyl alcohol extracts; solution of the residue in 0.1 N. sodium hydroxide; a second fourfold extraction with butyl alcohol using in this instance amounts of alcohol totaling 60 c.c.; evaporation to dryness again under reduced pressure; precipitation twice by acetone from the aqueous solution of the residue; solution of the second precipitate in hot 95 per cent ethyl alcohol; evaporation to dryness in a weighed beaker and finally a weighing of the white pregnandiol crystals.

Six pregnant women, four multiparas and two primiparas, were selected for study.

Consultation was carried out at regular intervals with each patient in order to acquaint her with the reason for the study and to impress upon her the need for cooperation.

A thorough briefing was made of all personnel who would or might have contact with the patient. This included resident staff, nursing force, and floor attendants.

From five to ten single 24-hour urine specimens were collected, nine to 24 hours apart, by the patient while at home before admittance to the University of Illinois Hospitals, and these specimens were brought directly to the hospital Outpatient Obstetrical Dispensary where they were placed in an icebox prior to assay.

Each patient was admitted to the Inpatient Obstetrical Division seven to ten days prior to the expected date of confinement. Here the collection of a daily 24-hour urine specimen was continued. By this method, at least three specimens of urine were on hand; the one currently under assay, a preceding 24-hour specimen collected in three eight-hour quantities, and the specimen then being collected from the patient.

At the onset of labor the immediate 24-hour specimen was stopped and a new specimen begun. Fractional catheterized specimens were collected during labor. An indwelling catheter was used during the postpartum period.

Forty-six (46) assays were completed for study.

Sample melting points of the compound obtained from assay were taken. These came within the range for sodium pregnandiol glucuronide, namely, 240 to 270 degrees.

Results

It was found that the urinary excretion of pregnandiol during the last weeks of pregnancy dropped from a maximum daily output of 40 to 100 mg. to a comparatively low level of 20 to 40 mg. At a point some 72 to 24 hours prior to the onset of labor, pregnandiol excretion reached its lowest ebb but had not disappeared from the urine. Because of this trend, we anticipated that by the time labor had actually begun the urinary excretion of pregnandiol would be minimal or would be absent from the urine altogether. At this point, however, we were surprised to find that the amount of pregnandiol excreted did not fade from the urine but instead rose sharply and during the 24-hour period immediately prior to the onset of labor, the quantity of pregnandiol actually reached levels ranging from 26.4 to 121.7 mg. and compared favorably with the amount excreted during the most active period of pregnandiol excretion. Not only was pregnandiol excreted prior to the actual onset of labor but it was subsequently found in the urine throughout the course of labor in appreciable amounts and did not disappear entirely until some 24 to 72 hours following delivery.

TABLE I. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para ii, Gravida iii, Delivered Ten Days Before Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	17 days before labor	49.0	2,675
24	13 days before labor	54.0	2,316
24	9 days before labor	65.0	2,080
24	3 days before labor	66.2	2,300
	3 hours of labor		
24	3 days after labor	0.0	1,750
24	46 days after labor	0.0	1,500

TABLE II. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para iii, Gravida iv, Delivered Nine Days Before Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	8 days before labor	61.8	1,630
24	5 days before labor	51.3	1,512
24	before labor	77.5	1,525
	2 hours of labor		
24	after labor	0.0	2,270
24	5 days after labor	0.0	1,975

TABLE III. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para i, Gravida iii, Delivered Three Days Before Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	9 days before labor	68.0	2,475
24	4 days before labor	51.0	2,130
24	2 days before labor	47.0	2,240
24	before labor	121.7	2,369
	3 hours of labor	8.7	385
24	after labor	40.1	5,190
24	3 days after labor	0.0	1,890

TABLE IV. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para i, Gravida ii, Delivered Five Days After Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	24 days before labor	104.0	970
24	22 days before labor	100.0	915
24	20 days before labor	92.0	980
24	17 days before labor	86.0	1,125
24	8 days before labor	68.9	750
24	7 days before labor	64.5	960
24	3 days before labor	63.3	640
24	before labor	115.0	835
	5 hours of labor	17.6	285
24	after labor	2.8	1,105
24	6 days after labor	0.0	1,450

TABLE V. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para 0, Gravida i, Delivered Four Days Before Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	12 days before labor	68.7	1,575
24	9 days before labor	71.7	220
24	3 days before labor	41.3	3,990
24	2 days before labor	13.8	2,290
24	before labor	26.4	2,400
	8 hours of labor	4.2	1,850
24	after labor	0.0	2,220

TABLE VI. PREGNANDIOL EXCRETION AT THE TIME OF LABOR
(Para 0, Gravida i, Delivered 20 Days After Term)

DURATION OF SPECIMEN (HOURS)	WHEN COLLECTED	PREGNANDIOL EXCRETED (MG.)	URINE PASSED (C.C.)
24	27 days before labor	34.0	3,880
24	25 days before labor	40.7	2,810
24	22 days before labor	46.7	3,675
24	20 days before labor	45.5	3,620
24	16 days before labor	48.8	2,220
24	7 days before labor	25.3	1,620
24	2 days before labor	31.3	2,050
24	before labor	37.3	2,460
	20 hours of labor	40.6	1,310
24	after labor	0.0	2,100

Comment

Although the quantity of prgenandiol excretion varied in each patient analyzed, the general trend of excretion was uniform; that is, there was a distinct drop, sometimes of a dramatic nature, during the last weeks of pregnancy, a leveling off phase, followed by a rise in excretion prior to labor, a continued excretion of pregnandiol during labor and its absence from the urine within a relatively short time following delivery. This trend was modified to some extent by the amount of pregnandiol excreted daily. If, on the average, large amounts of pregnandiol were excreted during the peak phase, that is, from 80 to 100 mg., the drop in excretion during the last weeks did not reach the low level seen in those cases where the excretion curve during the peak phase was comparatively small, namely, from 40 to 60 mg. This observation was illustrated in Case 4, when the peak pregnandiol output totaled 104 mg. and the leveling off phase revealed an excretion of 63.3 mg. daily, whereas, in Case 6, when 48.8 mg. were excreted, the leveling off phase showed an excretion of 25.3 mg. These levels suggest an average drop of from 25 to 40 mg. of pregnandiol before the leveling off phase.

All six patients showed a definite increase in pregnandiol excretion in the 24 hours immediately prior to labor, ranging from a comparatively low level of 26.4 mg. in Case 5 to a high output of 121.7 mg. in Case 3. Oddly enough, the patients who had the lowest prelabor pregnandiol excretion had the longest labors and were primiparas. In Case 5, a primipara, the prelabor output of pregnandiol was 26.4 mg. and lasted eight hours, and in Case 6, the other primipara, the prelabor pregnandiol output was 37.3 mg. and her labor lasted 20 hours. It is significant to note also that Case 6 delivered three weeks past the term date and at no time was her pregnandiol output especially high. The peak excretion was recorded on the sixteenth day before labor, a period four days

after the term date, at 48.8 mg. At this time the patient had an irritable uterus and the cervix on rectal examination had softened. Labor was anticipated because there had been a gradual rise in pregnandiol excretion during the preceding ten days from 34.0 mg. daily to the 48.8 mg. mentioned. Labor, however, did not develop. Instead there was a fall in pregnandiol output to reach a new low of 25.3 mg. seven days prior to the onset of labor. Again there was a gradual rise to 37.3 mg. in a 24-hour specimen. At this point labor began and lasted 20 hours, during which time 40.6 mg. of pregnandiol were excreted.

The low amounts of pregnandiol in the primiparas studied may reflect a tardiness of progesterone metabolism, allowing the stored-up progesterone to hold the uterine contractions in abeyance longer than generally expected. This deduction seems reasonable because in the multiparas investigated all excreted large amounts of pregnandiol in the 24 hours prior to labor and all had short labors. For example, in Case 1, 66.2 mg. were excreted and the patient developed a three-hour labor; the patient in Case 2 excreted 77.5 mg. and had a two-hour labor; in Case 3, 121.7 mg. were excreted and there was a three-hour labor; while in Case 4 a five-hour labor followed the excretion of 115.0 mg.

Several questions arise at this time. If primiparas characteristically excrete smaller amounts of pregnandiol throughout pregnancy and have smaller prelabor rises, will they have shorter labors if on occasion they excrete large amounts of pregnandiol? If multiparas characteristically excrete large amounts of the substance, will they conversely have prolonged labors if perchance they excrete comparatively small amounts of pregnandiol? It has been a time-honored custom to teach that primiparas have longer labors because in them the cervix and perineum yields slowly because those structures have not been stretched by previous childbirth.

It would be interesting to review pregnandiol assays conducted just prior to labor from a large number of patients to see if assay figures, from 60 to 100 mg., were on the whole obtained from multiparas, and if smaller outputs, in the 30 to 60 mg. range, came from primiparas. Or to be more inclusive, do low levels of pregnandiol excretion during the last six weeks of pregnancy necessarily indicate longer labors, regardless of the multiparity?

In four patients pregnandiol was excreted in appreciable amounts while labor was in progress, from a low of 4.2 mg. in Case 5 extracted from 220 c.c. of urine during an eight-hour labor, to a high of 40.6 mg. in Case 6 from 1,310 c.c. of urine during a 20-hour labor. From a total of 2,200 c.c. of urine passed in 36 hours of combined labor from four patients, 71.1 mg. of pregnandiol were obtained. This would be roughly 46 mg. in a 24-hour labor and would compare favorably with the average daily output of pregnandiol during the last weeks of pregnancy. So it can be seen that pregnandiol excretion while labor is in progress is of sufficient quantity to invite attention. All six patients had negligible amounts of pregnandiol in their urine within a few days after delivery. This observation points to the placenta as playing a leading role in the production of progesterone and its subsequent excretion as pregnandiol. In Case 3, 40.1 mg. were extracted in 24 hours immediately after labor. This amount was secured, however, from 5,190 c.c. of urine.

By arranging the 46 assays from all patients on a simple graph, it was possible to plot a curve of pregnandiol excretion for the peak output phase, for the low leveling off phase, for the rising phase immediately before labor, for the labor phase, and for the phase following delivery (Fig. 2). The average peak excretion is placed at 70 mg., the average leveling off phase at 35 mg., that immediately preceding labor at 65 mg., during labor at 25 mg., and after labor at 10 mg.

Aside from the observations that pregnandiol does not seem to disappear from the urine prior to labor, that it is actually on the increase as labor gets under way, and is even excreted while labor is in progress, we should like to comment further on several interesting trends of pregnandiol excretion detected during this study.

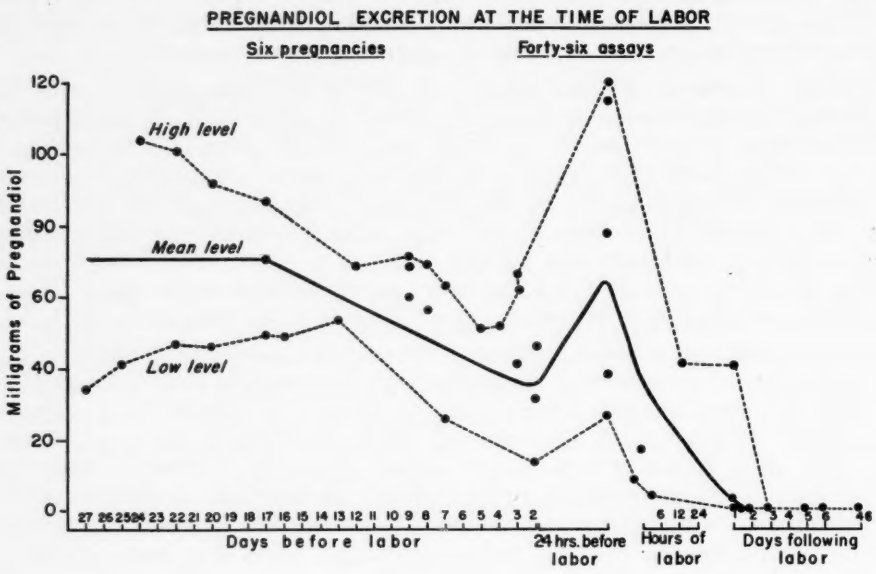

Fig. 2.

Venning and Browne,[7] in 1940, reported on the excretion of pregnandiol following the injection of progesterone and called attention to a time relationship between the onset of progesterone medication and the point of maximum pregnandiol output. In their studies as much as 48 to 72 hours passed before appreciable amounts of pregnandiol appeared. Allen and co-workers[22] experienced a comparable observation in 1944 when they published a series of pregnandiol assays following the administration of oral progesterone, anhydrohydroxy-progesterone. Although there was a slight increase in pregnandiol excretion following the first day, a maximum recovery did not occur until after the second day. Lyon[21] in 1946 also referred to the possibility of a delayed appearance of increased pregnandiol excretion following progesterone therapy.

These observations suggest the presence of a physiological time lag of some 36 to 72 hours from the point of progesterone ingestion until its metabolism is reflected in the urine by increased pregnandiol excretion. If it is possible to have a physiological time lag following the ingestion of therapeutic progesterone, the question immediately arises as to the possibility of a time lag when the seat of physiologic progesterone activity, the corpus luteum or placenta, starts to deteriorate.

Are all pregnandiol assays, therefore, from 36 to 72 hours off schedule? Is this observation of sufficient note to question the value of pregnandiol assays so far as diagnosing threatened abortion and therapeutic response to progesterone therapy are concerned? If there is a time lag of 36 hours or more from the point of increased or decreased progesterone activity within the body mechanism, until that change can be reflected in the urine through a corresponding rise or fall of pregnandiol excretion, then pregnandiol assays as a means to measure the seriousness of threatened abortion, and to measure the effectiveness

of progesterone therapy should be re-evaluated, because, by the time urine can be collected, and assayed, and substitution therapy started, damage already has been done, possibly beyond repair. Furthermore in our studies, a surprising amount of pregnandiol was found in the urine immediately prior to labor, and appreciable quantities were even obtained while labor was in progress. This may well be reason enough to suggest a review of those pregnandiol studies which showed normal or increased excretion values in threatened abortion and premature labor which were interpretated at the time, because of the comparatively high pregnandiol output, as a favorable prognostic sign. It could be that the comparatively high pregnandiol output was in reality an indication of imminent abortion or labor.

It is quite possible that the drop in pregnandiol excretion, during the last weeks or days of pregnancy which has been interpreted heretofore as the climax of pregnandiol excretion, is not the climax after all. We wish to offer the hypotheses that the real climax of pregnandiol activity comes just prior to the onset of labor, characterized by an excretion curve which turns sharply upward, at the peak of which labor occurs. Just what the explanation is for this sudden increased output of pregnandiol would be difficult to say without further study. Is this dramatic outpouring of pregnandiol the result of some physiological readjustment of pregnancy hormones secondary to imminent labor or does this phenomenon initiate labor itself?

Summary

Six pregnant women, four multiparas and two primiparas, had periodic studies of urine for pregnandiol, totaling 46 assays, covering periods involving the last weeks of pregnancy, immediately prior to labor, during labor, and following delivery. It was found that although the quantity of pregnandiol excretion dropped during the last weeks of pregnancy, the pregnandiol curve prior to the onset of labor rose sharply and continued at an appreciable level throughout labor, at the conclusion of which pregnandiol output fell to a negligible amount within 72 hours. A discussion of the possible significance of these findings was advanced and several suggestions were offered regarding further investigative work on pregnandiol excretion.

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Discussion

DR. R. R. GREENE.—The author has definitely demonstrated that there is no drop in pregnandiol excretion immediately preceding and at the onset of labor. I am inclined, however, to doubt the significance of some of the more minor variations in his data and a few of his speculations. These, however, I will leave for Dr. Davis to discuss later.

Dr. Venning in the October, 1948, issue of the *Gynecologic and Obstetrical Survey* discussed this subject and gave the data on nine patients. She had a comparable number of pregnandiol determinations in the period preceding labor in three patients. Her findings were similar in that there was no drop in pregnandiol excretion preceding the onset of labor.

Dr. Mauzey has not stressed the true significance of his results. As I see it, it is another nail in the coffin of the too widely accepted ideas on the hormonal causes of the onset of labor.

To be specific, it is widely believed and taught that estrogens stimulate or cause uterine contractions and that progesterone inhibits or prevents uterine contractions. The onset of labor is therefore due to the fact that as term approaches there is a drop in progesterone, the inhibiting factor, and an increase in estrogens, the stimulating factor.

Belief in this theory necessitates among other things evidence that (a) progesterone inhibits or prevents uterine contractions and (b) that progesterone production falls to low levels prior to the onset of labor.

The early works on the effects of progesterone on uterine contractions was done in the rabbit. This was good work, but the almost universal early belief in its direct applicability to man was not justified. This direct application to man, by the way, ignored the fact that in other species such as the rat and the mouse progesterone does not inhibit uterine contraction and does not prevent the response of the uterus to pituitrin.

A little later it was claimed by some workers that progesterone inhibited uterine motility in the nonpregnant and the postpartum woman. This work was done with relatively crude extracts of the corpus luteum, later with crystalline progesterone, and even with aqueous extracts of the corpus luteum. Progesterone, it might be added, is quite insoluble in aqueous solutions, and it seems very likely that the inhibiting effects of the aqueous solutions of the corpus luteum on uterine motility were due to the chlorobutanol present in the solution as a preservative. This latter substance, by the way, is a rather potent pharmacologic agent in inhibiting uterine contractions.

The uterine motility studies in the human being were repeated by later workers, particularly by Moir, Kurzrok, Bickers, and Henry and Browne. I think that they have clearly demonstrated that, under the influence of progesterone, regular contractions of high amplitude occur in the uterus. While under the influence of estrogens there are small irregular contractions of the uterus.

The early work on excretion of pregnandiol in pregnant patients near term included assays done at widely spaced intervals. The conclusion drawn from these early works was that the pregnandiol excretion falls off before term. This fitted in very well with the accepted theory as to the cause of labor.

The work reported here this evening and that of several other recent workers show that pregnandiol excretions do not drop prior to the onset of labor. There is no good evidence, therefore, that progesterone production decreases immediately prior to the onset of labor.

Frankly, I don't know what causes the onset of labor. I don't know exactly what effects the hormones have, if any, but I think we had better revise our thinking and teaching that hormonal changes are the immediate cause of the onset of the labor.

DR. M. EDWARD DAVIS.—The data presented by the author on pregnandiol excretion during labor are exceedingly interesting. The number of cases studied, however, is too small to warrant any conclusions. Serial determinations during the last several months of the gestation and subsequent labor will be necessary to confirm some of the observations recorded. There is such a marked variation in the daily excretion of metabolite in the same patient that many quantitative studies will be necessary to answer some of the interesting questions raised by the author.

Urinary pregnandiol is the metabolite of progesterone activity and its quantitative determination is a measure of available steroid. During the first trimester of pregnancy it represents the activity of the corpus luteum. However, with the development of the placenta most of the steroids are elaborated by this organ. In the typical patient the daily excretion during the corpus luteum phase may average 10 to 15 mg. a day. However, the introduction of the placental phase of steroid production is followed by a progressive increase in the daily outut of pregnandiol, leveling off during the last month of the gestation.

We can confirm the author's findings that the onset of labor does not necessarily coincide with a drop in the urinary titer of pregnandiol. In most of our patients who were studied no marked variation in the daily excretion of pregnandiol preceded the onset of labor. In some of our patients who were investigated because of habitual abortion, the evacuation of the uterus occurred at a time when the curve of this metabolite was rising.

Early death of the gestation may be reflected in a drop in the daily excretion of the pregnandiol. This represents failure of the corpus luteum because the degenerating chorion does not provide the necessary gonadotropin to maintain the corpus luteum. These changes are slow in developing so that the excretion of urinary pregnandiol after the death of the conceptus will decline slowly. No single determination should be used to diagnose missed abortion. The continued output of decreasing amounts of pregnandiol is good evidence of death of the gestation.

Death of the fetus in mid-pregnancy is followed by a gradual decline in the output of pregnandiol. We have followed serial determinations as long as six and eight weeks after intrauterine death, during which there is a slow but continued drop in the daily excretion of this metabolite. This slow reduction probably corresponds to the retrogressive changes in the vascularity and function of the placenta which follow fetal death.

In the author's further studies on this interesting problem we would suggest that he carry out duplicate determinations by the Venning method and the method for free pregnandiol. The latter procedure will eliminate other glucuronides than sodium pregnandiol glucuronidate and may throw additional light on the metabolism of progesterone.

DR. JOHN I. BREWER.—This is a measure of excretion, not production. I wonder if the excretion rate of this substance may not vary. The kidney may simply release the substance in greater or lesser amounts which may not be completely in accord with the secretion rate. There is a fall in excretion as noted in the chart, and that is followed by a rise. The rise may simply represent the ability of the kidney to let go of something that was not needed.

I had in mind the same thing Dr. Greene mentioned, whether they had measured any of these substances in the patients in whom they induced labor at eight or eight and one-half months. Is the curve the same in those that were induced and in those that went into labor normally and spontaneously? Also in cesarean section done without labor, were there follow-up studies and does this substance disappear at the same time as it does after normal labor?

DR. HENRY S. GUTERMAN.—Although I have not studied the excretion of pregnandiol in the last few days of pregnancy before labor as closely as Dr. Mauzey, I have found no consistent relationship between the level of pregnandiol and the onset of labor. If pregnandiol is a reliable index of progesterone elaboration and does not resolve the question of the relationship of progesterone to the onset of labor, it is possible, as Dr. Greene suggested, that factors other than variation in progesterone secretion may be responsible for the initiation of labor.

The relationship between progesterone administration and pregnandiol excretion merits a few words. To date, it had been shown that when anhydrohydroxy-progesterone (''oral progesterone'') is administered orally, pregnandiol is not excreted in the urine. The administration of crystalline progesterone by mouth or by intramuscular injection is followed by the excretion of considerable amounts of pregnandiol. The rate of excretion depends on the route of administration as well as the medium in which the progesterone is administered. If progesterone is swallowed or injected as a solution in oil, pregnandiol appears in the urine in 12 hours and its excretion ceases about 24 to 36 hours later. When progesterone is administered intramuscularly as an aqueous crystalline suspension, pregnandiol excretion begins about 24 hours after injection and lasts for a longer period. However, from the excretion of pregnandiol after progesterone administration, we have no proof of a functional effect of the progesterone.

DR. MAUZEY (Closing).—It seems to me as a clinician who went into the laboratory for a period of time that the subject of progesterone metabolism needs to be reviewed and perhaps some work previously done needs to be done over again. There is strong evidence to support the contention that we are dealing with a king hormone which, with very little change in its basic structure, may be switched from one substance to another such as is seen in the change from progesterone to pregnandiol.

As to correlating the condition of the cervix and uterus with pregnandiol excretion, we did that in each case. There was no definite correlation between changes in the uterus and cervix and in pregnandiol excretion except in one case. In this case we thought labor was going to occur because of an increase in the pregnandiol level together with a concomitantly irritable uterus and softened cervix. Labor did not develop, however, and the pregnandiol excretion dropped, the uterus relaxed, and the cervix returned to a thickened condition, but in a few days the cervix softened up again and the pregnandiol excretion rose, at which time labor finally developed. In that case we believe we did get a relationship; in others we did not. We expected to find a correlation between pregnandiol excretion and uterine changes, and were disappointed. We have had no experience with pregnandiol when the amniotic sac ruptured prematurely. As far as the excretion of pregnandiol with cesarean section is concerned, Lyon measured pregnandiol output at that time and he found no significant change. Allen of St. Louis reported on a case following cesarean section in which the placenta was allowed to remain in the uterus. Interestingly enough, fairly large amounts of pregnandiol continued to be excreted for a number of weeks.

HYPERROTATION AND DEFLEXION OF THE HEAD IN BREECH PRESENTATION*

With a New and More Descriptive Terminology for Breech Presentation

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VARIATIONS in fetal attitude occurring in breech presentation are well known. These include: complete (full) breech, incomplete (frank) breech, footling and knee presentations, all of which arise from varying relationships between the lower extremities and the spine. In addition, there are varying relationships between the fetal head and/or the upper extremities and spine. Fetal attitude in utero can be fully appreciated only by roentgenographic studies. This is especially true with reference to the fetal head and spine.

Excellent x-ray studies have been made in the past. Warnekros[1] in 1919 published a magnificent atlas of roentgenographic plates of fetal presentations, positions, and attitudes. Brakemann[2] (1936) was concerned specifically with the relationship of the fetal head to the spine. He showed that the head was well flexed in only 22 per cent of patients and hyperextended in 11 per cent. Stein[3] (1941) studied deflexion attitudes and called attention to the frequency of frank breech. He advocates careful scrutiny of roentgenographs to determine the extent and degree of deflexion in order to anticipate difficulties which may be encountered. More recently, Wilcox[4] (1949) has drawn attention to the deflexed head and to the frequency and significance of deflexion attitudes. In all these studies there are only two passing references to hyperrotation and deflexion of the head. The first was by Warnekros (Fig. 1) and the second by Stein. Standard textbooks are silent on the subject.

Recently we have had two patients whose babies, presenting by the breech, manifested this peculiar attitude of hyperrotation and deflexion of the head. The management of the first patient presented a perplexing problem because of our unfamiliarity with this fetal attitude. The patient was delivered by elective cesarean section in the belief that we were dealing with an unusual pathologic condition which might lead to insurmountable dystocia or to fetal asphyxia during labor. Encountering the same condition in a second patient within fifteen months indicates that such attitudes probably are not rare. Two additional instances of this peculiar attitude have since been brought to our attention.

CASE 1.—Mrs. A. C., a 22-year-old primigravida, entered Michael Reese Hospital in mild labor on Dec. 5, 1946, seven days before her estimated delivery date. On the day preceding admission, a routine roentgenograph of the abdomen revealed a full-term fetus in left sacrum transverse position. The fetal head was rotated and deflexed so that the face seemed to point toward the fetal back (Fig. 2). Several possibilities were considered in attempting to explain this peculiar fetal attitude. The most probable cause seemed to be a tumor of the neck, such as a congenital goiter. Next in our consideration was the possibility of several loops of cord being wrapped around the fetal neck under sufficient

*Presented before the Chicago Gynecological Society, Dec. 16, 1949.

tension to produce extension and rotation. Finally it was considered to be some unrecognizable form of fetal anomaly. It did not appear to us that this fetal attitude could and would correct itself. A low cervical cesarean section was performed under inhalation anesthesia. Incision of the lower uterine segment and evaluation of the fetal attitude and position revealed a full-term male fetus in complete breech presentation, with the fetus lying in complete flexion and the chin resting on the chest. The baby weighed 3,120 grams and was perfectly normal in all respects.

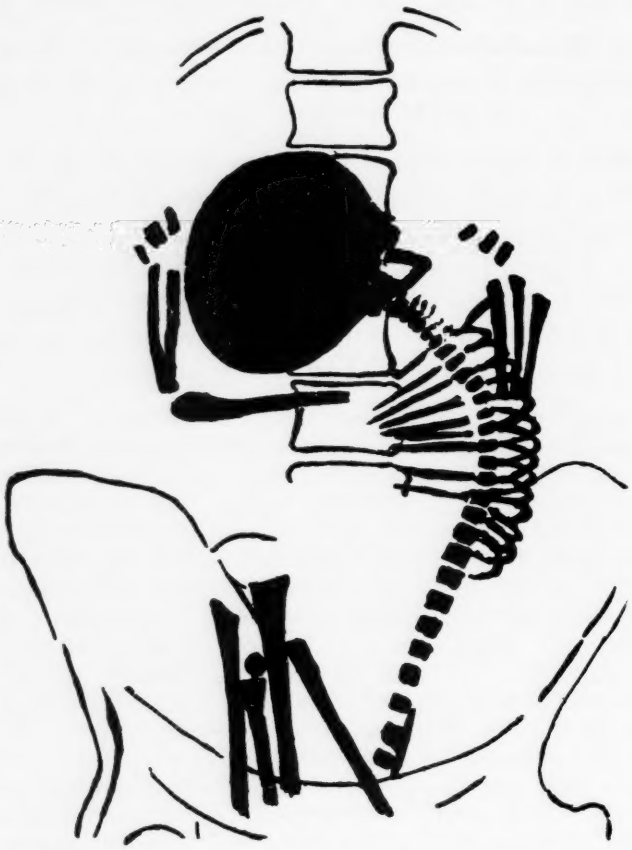

Fig. 1.—Hyperrotation and deflexion of the head. (Warnekros.)

CASE 2.—Mrs. S. S., a 37-year-old gravida ii, para i, was admitted to Michael Reese Hospital on Jan. 28, 1948, one week before her estimated delivery date, because of breech presentation and suspected cephalopelvic disproportion. Roentgenograph on Jan. 30, 1948, revealed a full-term fetus in left sacrum position with the head deflexed and rotated so that the occiput pointed toward the chest (Fig. 3). The attitude of this fetus seemed to be identical with that in Case 1. Because of our previous experience, the patient was examined again roentgenographically four days later. At this time the fetus was found to have undergone spontaneous cephalic version, and was presenting as a well-flexed occiput transverse (Fig. 4). One week later labor began spontaneously. After a 5-hour, 10-minute first stage and 27-minute second stage, a 3,100 gram male infant was delivered by outlet forceps. The child was normal in all respects.

The sequence of events in Case 1, which resulted in a spontaneous correction of the fetal attitude, prompted us to be more complacent in the manage-

ment of Case 2. In the second instance there was not only a restoration of the normally poised head but also a spontaneous cephalic version, which resulted in simple delivery one week later as a left occiput anterior.

It has been our privilege to obtain two additional roentgenographs of similar attitudes from Dr. I. F. Stein (see Fig. 5 for one). These patients were delivered vaginally without difficulty and no fetal anomaly was encountered.

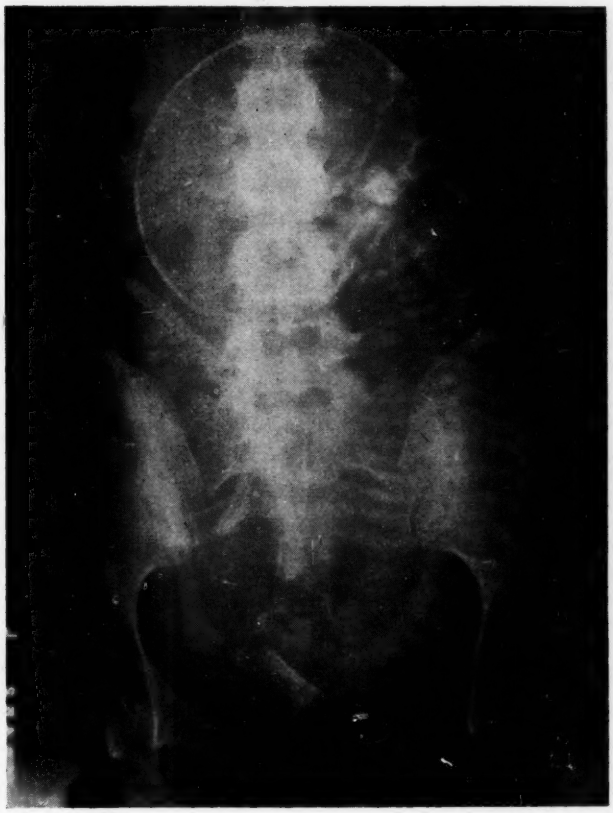

Fig. 2.—Case 1. Hyperrotation and deflexion of the head, legs extended.

In the light of these experiences it would seem advisable to manage hyperrotation and deflexion of the fetal head in breech presentation by close continued observation rather than active interference. Such a "hands-off" policy will probably result in spontaneous correction either before or during labor. There would seem to be no additional danger of dystocia or of fetal death when hyperrotation and deflexion of the head are present.

There is much to learn concerning the reasons for breech presentation and the various fetal attitudes. Gravitational influence on ultimate presentation is no longer considered important. It is accepted that anything which interferes with the normal feto-uterine accommodation may lead to other than cephalic presentation. Thus, if the uterus is arcuate, septate, bicornuate or distorted by tumors or another fetus, the fetus may accommodate better as a breech. A low-lying placenta or small pelvis may have a similar effect. The

presence of fetal abnormalities—hydrocephalus and anencephalus, multiple fetuses, and hydramnios—may predispose to "ultimate" breech presentation. The incidence of breech presentation during the second trimester of pregnancy greatly exceeds that found at term. Presentation usually does not change after the thirty-fourth week of gestation although spontaneous version is known to occur during labor.

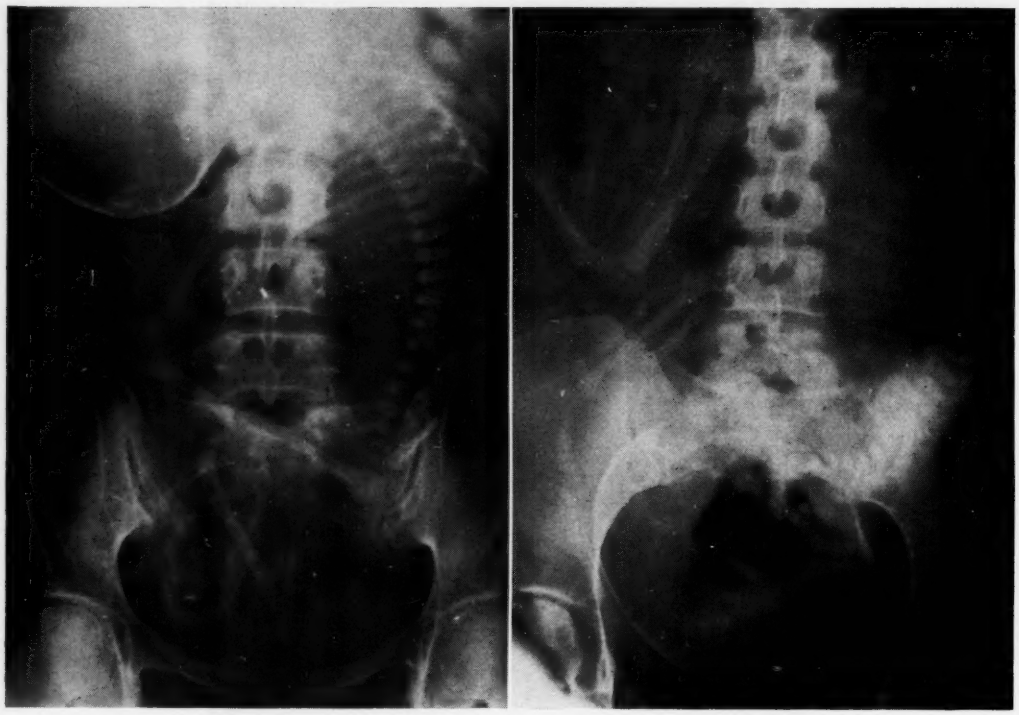

Fig. 3. Fig. 4.

Fig. 3.—Case 2. Hyperrotation and deflexion of the head, legs flexed.
Fig. 4.—Case 2. Spontaneous cephalic version four days later.

The word "ultimate" is used to denote the presentation and position at the onset of labor. "Ultimate" also may be applied to attitude. We have demonstrated that both attitude and presentation may change when labor is imminent. Hence if roentgenographs are to be of greatest value they must be taken when the patient is in labor. Roentgenographs taken some days before the onset of labor should not be allowed to overinfluence the management of the patient. Most roentgenographic surveys of attitude in breech to be found in the literature can be criticized from this viewpoint. Attitude, even more than presentation, may change, and decisions reached from the study of roentgenographs taken at the thirty-seventh or thirty-eight week of gestation frequently are not applicable at the onset of labor.

Prematurity often is referred to as a predisposing factor in breech presentation, but it seems more logical to accept prematurity as coexistent rather than as responsible for the breech presentation. The fetus is free to gyrate

at will during early pregnancy. This also holds near term when the fluid is excessive. Usually, however, as the fetus grows, it becomes more confined by the uterine walls. This is particularly true if the amount of liquor amnii is scant.

Vartan[5] has shown that the commonly accepted etiological factors could be demonstrated in only 7 per cent of breech presentations, if prematurity and multiple pregnancy were eliminated. Although it has been recognized that

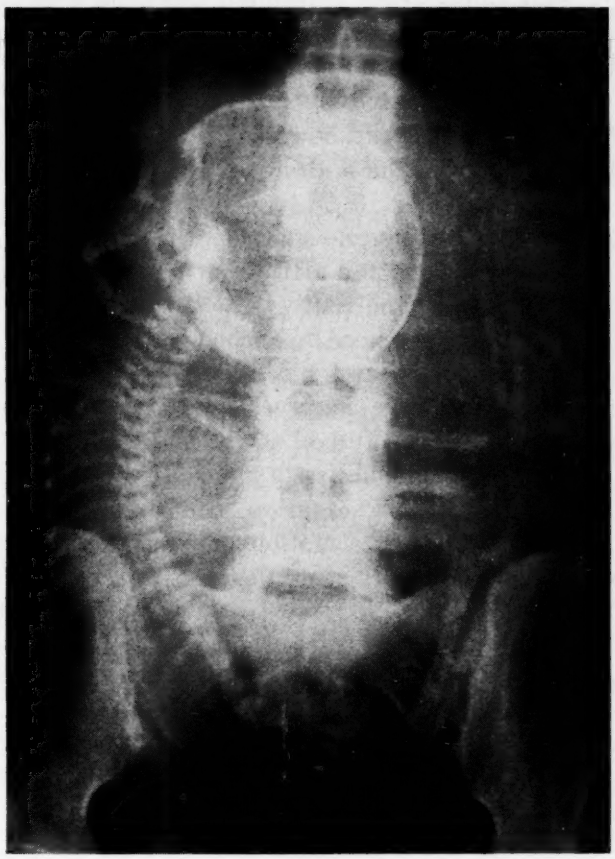

Fig. 5.—Hyperrotation and deflexion of the head; back and sacrum directed toward right.

extension of the legs is a primary fetal attitude in breech presentation, Vartan (1940) apparently was the first to call attention to the possibility that such extension can interfere with spontaneous cephalic version. Extension of the legs was noted in 7.3 per cent of the cases studies. Stein,[3] Henderson,[6] and others have found such extension in over 50 per cent. Tompkins[7] considers extension of the legs, an inactive child, and impaired motor mechanism as important etiological factors in breech presentation.

On the other hand, Vartan also has shown that leg extension does not necessarily prevent spontaneous version nor preclude external version—although the latter is known to be more difficult when the legs are extended. Thus it appears that ultimate breech presentation results from interference with the free motion of the fetus in the majority of instances. Extension of the legs on the thighs eliminates the downward thrust that might lead to spontaneous

cephalic version. How do the legs become extended when flexion provides a more compact ovoid? This is probably due to chance. Normal fetal movements in complete breech presentation may permit the legs to flay out toward the iliac fossa and be deflected upward by the uterine wall. Once extension has occurred, the uterine walls will tend to maintain this attitude, and prevent spontaneous cephalic version.

Deflexion of the spine and head likewise seems a matter of chance. It could be produced by transient fetal movement. If the forehead impinges on the fundus or placenta during such movement, the head may be carried gradually to full extension. By the same process chance movement alone can be responsible for the hyperrotation of the head presented here. That such an attitude may be transient is proved by our observations. Further it can be demonstrated that the head of the newborn child can rotate through an arc of more than 90 degrees from the midline on slight pressure without harm to the baby.

Some authors believe that muscle spasm—even though transitory—may be responsible for malpresentations and attitudes. Gibberd's[8] original suggestion has been applied by Knowlton[9] and Nagyfy[10] to explain hyperextension in transverse presentation. There is no need to theorize about muscle spasm—chance active fetal movement will account for occasional bizarre attitudes.

The terminology of attitude in breech presentation should be revised. The expressions "complete" or full and "incomplete" or frank breech are not sufficiently descriptive. It would seem more descriptive to refer to a breech presentation, a breech-footling presentation, a footling presentation, or a knee presentation. To complete the description of attitude, it seems advisable to add: legs flexed, legs extended, arms flexed, arms extended, spine flexed, spine extended, head flexed, head extended, or head rotated. Such information is rarely obtained without a roentgenograph. As now employed, extension of the legs may or may not connote deflexion attitude of the spine or head. In the past some authors have used the expression "deflexion" or "extension" very loosely to refer to deflexion or extension of the legs, or the spine, or the arms, or the head, or all four. The terminology here suggested seems preferable because of its specificity.

SUGGESTED TERMINOLOGY

Breech			*Legs*—Flexed / Extended
Breech-Footling—Single / Double			*Arms*—Flexed / Extended
Footling—Single / Double		*with*	*Spine*—Flexed / Extended
Knee—Single / Double			*Head*—Flexed / Extended / Rotated

Summary

Two instances of hyperrotation and deflexion of the fetal head in breech presentation have been described.

In both instances, spontaneous flexion and corrective counterrotation occurred before delivery.

Roentgenographs taken prior to the onset of labor should not be allowed to overinfluence the management of the patient.

The diagnosis of hyperrotation and deflexion of the fetal head in breech presentation does not seem to warrant active interference.

Such attitudes probably are the result of chance movements and require no corrective maneuvers.

The terms "ultimate presentation," "ultimate position," and "ultimate attitude" are suggested to denote the presentation, position, and attitude at the onset of labor.

The nomenclature of attitude in breech presentation has been discussed and a more specific terminology is suggested.

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Discussion

DR. H. CLOSE HESSELTINE.—Dr. Reis and Dr. DeCosta offer essentially two main points in their presentation. The first point about breech as the presenting part is an emphasis on the need for exact knowledge at the onset of labor; the second point concerns itself with a plea for a common terminology on breech classification.

With all the attention and discussion which have been presented on breech delivery, the fetal mortality and injury of those who survive still exceed that of vertex presentation. It is recognized generally that when the face is the presenting part, it is abnormal. Yet this occurs only one-sixth as often as does breech. I believe that, in every instance, breech should be looked upon as an abnormal situation if not as a pathologic situation. Such universal teachings and warnings might offer better safeguards to both the mother and the baby.

In the year 1925-1926, while I was at the University Hospital in Iowa City, a good x-ray picture of "breech" was desired for teaching purposes. A patient was found who had the breech as the presenting part. When the patient was sent to the roentgenological department the picture revealed a vertex. The following week the patient was again seen and again was thought to have a breech and this was confirmed by two other staff members. The patient was again taken to the x-ray department in a wheel chair and again it was a vertex. A few days later the same observations were noted but this time the patient was taken on a cart for the picture. This time a "breech" was found over the inlet. Afterward the patient was put in the erect position and walked a short distance. Subsequently a picture showed that the pole had changed to a vertex. This amplifies and emphasizes the point that Drs. Reis and DeCosta stress, that the fetal attitude is subject to change, sometimes in a short period and possibly without an obviously particular provoking factor.

No doubt many obstetricians recognize but may not heed the point that the essayists emphasize: (1) that roentgenographs prior to the onset of labor must not unduly influence

the management of the patient; and (2) that variable and peculiar positions when the breech is the presenting part can await the onset of labor unless there are other obstetric indications for interference.

The proposals of Reis and DeCosta have real virtues, but I believe they have carried it to a complicated degree by introducing factors of the arms, spine, and head.

In conclusion, every contribution that can be advanced to reduce fetal injuries and lower the fetal mortality and, at the same time, reduce injury to the mother in the instance when the breech is presenting is most commendable.

DR. FREDERICK H. FALLS.—A similar deflexion attitude with backward bowing of the spine was described by me in 1915, and because no similar intrauterine fetal position had been previously described was given the name of "opisthotonos fetus." In this case, which presented transversely, after rupture of the membranes the heart tones suddenly disappeared. A breech extraction after version failed to recover a live baby. Our explanation was that the decompression of the uterus after rupture of the membranes resulted in cord compression due to its unprotected position because of the deflexion attitude of the fetus. After delivery there was no reason found, on careful physical examination of the baby including autopsy, to explain the opisthotonos position. Webster, DeLee, and Williams said they had not seen an x-ray demonstration of a similar case. Since that time I have seen several examples of this condition, some of which were breech and others cephalic or transverse presentations. Cesarean section may be indicated in such cases if spontaneous correction does not occur before or during labor.

DR. DE COSTA (Closing).—I am well acquainted with the findings of opisthotonos fetalis. There are many reports in the literature including those of Gibberd, Nagyfy, Knowlton, Kobak and others. However, we are not discussing opisthotonos fetalis. Opisthotonos is an extension of the spine and head, most often encountered in transverse presentations. In the condition we are discussing, the spine is well flexed and the head is hyperrotated and moderately extended. The two conditions are not the same.

A CLINICAL STUDY OF 240 INFERTILE COUPLES*†

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THE average infertile couple desiring children will consult a physician after a year or more has elapsed. It has been estimated that in about 85 per cent of all ailments the general practitioner is the first medical adviser. He, therefore, has the first chance to study infertility, and he probably overcomes this infertility in many instances. Couples who do not achieve a result find their way to the specialist; and, as all of us have experienced, they frequently go from one gynecologist to another, and too frequently they do not continue for a sufficient period to achieve even a complete diagnosis.

The literature is filled with studies of the problems of infertility. There has been a tremendous increase in our knowledge of endocrinology, chemistry, physiology, and also the psychology of the infertile couple in recent years. Basal body temperatures, vaginal smears, sperm studies, the influence of hyaluronidase, and many others, have been widely discussed, approved, and some have been subsequently rejected. The relief of psychosomatic problems as well as the correction of endocrine deficiencies are of great importance and have been given much publicity. It is, however, not the scope of this paper to discuss the merits and importance of all these rather new phases in the infertility field, but rather to present the clinical material studied and the observations made.

The material studied here represents 240 couples seen in an infertility clinic (Planned Parenthood Centers) which receives many patients referred by adoption agencies for a study prior to adoption proceedings, other couples referred by social agencies ,and some patients referred by private practitioners. Table I shows that out of 240 couples, only 55.8 per cent finished their study, i.e., remained under observation for at least one year. One hundred six couples, or 44.2 per cent, did not visit the clinic often enough and could not be encouraged to return. Table II shows the number of patients who completed their study, and in whom either pregnancy occurred in less than eighteen

TABLE I

	NO.	%
Patients, May, 1944, to May, 1948		
Completed study	134	55.8
Incomplete study (less than 1 year of observation)	106	44.2
	240	100.0

*This work was carried out at the Planned Parenthood Centers, Chicago area.
†Presented before the Chicago Gynecological Society, Nov. 18, 1949.

months from entering the clinic or in whom a diagnosis of the cause of their failure to conceive had been made within that period of study. A period of eighteen months was arbitrarily chosen as sufficient either to overcome the infertility or otherwise to determine the cause—or probable cause—of the failure.

TABLE II

	NO.	%
Patients who completed study	134	100
Pregnancies	35	26.1
Female sterility plus associated minor male factors in 14 patients	65	48.5
Male sterility plus associated female factors in 5 patients	34	25.4

Method of Study

A detailed general history is essential. A thorough physical and pelvic examination is followed by determination of the basal metabolic rate, Kahn test for syphilis, urinalysis, and a complete blood count. Subsequently, postmenstrual tubal insufflation (Rubin) and semen examinations are carried out. Results of previous patency tests done elsewhere are noted but never accepted as evidence of patent tubes. Supposedly closed tubes are found repeatedly to be patent. The reverse is also true. Occasionally the Rubin test shows narrowing of the tubes either on an anatomical basis or on the basis of spasm which can be relieved by spasmolytic drugs. For semen analysis the specimen should be collected and brought to the clinic in a cold-cream jar. The specimen should not be more than two hours old and should be obtained after at least four days of abstinence. Volume, motility, percentage of abnormal forms, presence of leucocytes and other cellular elements are studied and an accurate sperm count is obtained. If the semen is normal, the husband is ruled out as a potential cause of the infertile mating, provided that he is potent and that the sex habits are within normal range. If the first specimen is abnormal and repeat specimens show marked deviations from the normal, the husband is referred to an urologist. The fertile period is discussed with all patients, and they are all taught to keep a chart of their basal body temperature. This is continued for the entire period of observation. Endometrial biopsies are taken at least once from each patient and more often when indicated. Pregnandiol studies have been made on a series of patients to corroborate other ovulatory phenomena. Vaginal smear studies were carried out in some patients early in this study. They have been discontinued because it was felt that equal information was obtained from basal body temperature readings.

Results

Female Sterility (Table III).—Sixty-five patients, 48.5 per cent of the material, fall into this group. The average age in this group is 31.5 years, the average period of attempted pregnancy is seven years, both figures being slightly higher than in the group that achieved pregnancy.

Thirty-four patients in this group were found to have closed tubes. Closure was diagnosed either by repeated Rubin tests, and verified by studies with instillation of iodized oil, or by clinical findings of chronic pelvic inflammatory disease with a history of acute symptoms. In this latter group (8 of 34) no tubal studies were undertaken. In 9 of the 34 patients there was a definite his-

TABLE III. FEMALE STERILITY

Patients	65	100%	
Average age	31.5 years		
Average period of attempted pregnancy	7 years		
Previous full-term pregnancies	3		
Previous abortions (spontaneous and instrumental followed by infection)	9		
Etiology			*Associated Male Factors* (oligospermia of 20-50 mil. per c.c.)
Closed tubes, with or without clinical symptoms of P.I.D.	34	52.3%	8
Multiple fibroids	10	15.4	2
Absent tubes (previous surgery)	1	1.5	
Endometriosis	1	1.5	
Hypoplastic uterus	3	4.7	2
Anovulatory cycles	9	13.9	2
Eunucoid with amenorrhea	1	1.5	
Carcinoma of cervix	1	1.5	
Polycystic ovaries with oligomenorrhea	1	1.5	
Unknown	4	6.2	
	65	100.0%	14

tory of postabortal infection. Three other patients in this group had had a full-term pregnancy six to fourteen years previously.

Ten patients were found to have multiple fibroids the size of a ten weeks' pregnancy or larger. In none of these was conservative surgery, i.e., myomectomy, feasible. One of these patients had had a full-term pregnancy ten years previously.

One patient looking for relief from her sterility was unaware that both tubes had been removed at a previous operation. This became known only when a detailed operative report was obtained.

One case of endometriosis was encountered in this series. This patient was not operated on, but the diagnosis was based on typical clinical symptoms and findings.

Three patients with a hypoplastic, i.e., small uterus, had markedly narrowed tubes, as evidenced by repeated Rubin tests where only small amounts of carbon dioxide passed at pressures above 120 mm. in spite of spasmolytic drugs. Lipiodol studies of these patients confirmed the findings. Additional male factors in two patients and lack of continued interest on the part of the patient may have played a role in this small group.

Three patients had cervical erosions which were treated by electric cautery.

Nine patients with otherwise normal findings showed constant anovulatory cycles by temperature charts, biopsies, and pregnandiol studies. These patients were not influenced by any hormonal therapy employed.

One patient presented an eunuchoid type of ovarian dysfunction with a primary amenorrhea.

One patient was found to have an early squamous-cell carcinoma of the cervix.

One patient with a marked oligomenorrhea and polycystic ovaries had a bilateral ovarian resection and became pregnant two months later. During a virus infection a spontaneous abortion occurred at two months. The patient did not return but it was learned that she underwent a hysterectomy about nine months later, for reasons unknown to us.

In four patients no factors responsible for the infertility were discovered.

Associated male factors in the form of mild oligospermia were found in 14 cases (Table III), an incidence of slightly more than 20 per cent. The female factors were, however, so dominant that the seminal findings are mentioned only as associated pathology in these cases.

Male Sterility.—There were 34 couples, 25.4 per cent, in this study, in whom the failure to conceive was traced to the male partner. The age distribution, the number of physicians previously seen, and the period of involuntary childlessness differ only slightly and insignificantly from other groups in this study. In only one couple had a previous pregnancy resulted. All others were primary infertility problems for this mating. Several women in this group had had pregnancies or abortions in a previous marriage or premaritally.

All patients in this group displayed either a marked reduction (less than 15 million per cubic centimeter) or a complete absence of spermatozoa in repeat examinations. Most of these men were subsequently seen by urologists, who verified the findings. There has been no instance where urological treatment has reversed an azoospermia or improved an oligospermia of less than 5 million per cubic centimeter. Mild oligospermia as well as pyospermia have responded well to local and systemic therapy. Here thyroid therapy has been the stand-by. Gonadotropins and testosterone have not been used in this series. No further work-up was carried out in this group when urological care was refused or the urologist's prognosis was poor. Several husbands refused sufficient cooperation for repeat examinations, and likewise refused any therapy. Twenty-nine female partners in this group presented normal findings. Two had cervical erosions and another one a small cervical polyp. One patient had a hypoplastic genital status. Another had such a narrow, tortuous cervical canal that a patency test could not be carried out. Another patient had several negative Rubin tests. and long tortuous tubes of the infantile type were found on x-ray visualization. The husbands of these five patients were azoospermic, and these cases are carried as male sterility since the female factors were of secondary importance. Fifteen per cent, then, of the male sterilities had associated female factors.

Comment.—More than 50 per cent of the female as well as the male sterility group had been seen and treated by two or more physicians without receiving the benefit of a diagnosis and a definite answer to their problems, even though that answer could have been given in these instances. In numerous instances the women had received hormone therapy without investigation of the husband, who subsequently showed an azoospermia.

TABLE IV

35 Pregnancies, 26.1%	
Age	22-36
Average age	29.7 years
Married without use of contraceptives	1-11 years
Average	4.9 years
Previous full-term pregnancies (8 and 12 years ago)	2 patients
Previous spontaneous abortions (2, 5, 15 years ago)	3 patients
Habitual abortion	0

Pregnancies (Table IV).—Thirty-five pregnancies occurred in patients between 22 and 36 years of age, the average age being 29.7 years. The period of marriage without the use of contraception ranged from one to eleven years, with an average of 4.9 years. Only two patients had had previous full-term pregnancies, eight and twelve years before, respectively. Three patients had

had one spontaneous abortion, two, five, and fifteen years before, respectively. Habitual abortion was not encountered in this series. One patient had not consulted a physician prior to coming to the clinic. Eighteen patients had been under the care of one physician each, six patients had each seen two doctors, and nine patients had consulted with three physicians each before entering the clinic. One patient had been under the care of four physicians for her sterility. In most instances the history revealed incomplete infertility studies together with multiple hormone therapy.

Eight of the 35 patients gave a history of some menstrual irregularity. Two of these menstruated every five to seven weeks, the other six having periods three to five weeks apart. Only one patient in this group displayed any physical findings which might be construed as "endocrine stigmata." This patient had a moderate girdle obesity, facial and chest hirsutism, a deep voice, and a funnel pelvis. Her menstrual history was normal, the basal metabolic rate +5 per cent. (She developed a hypertensive toxemia and was delivered by cesarean section at 38 weeks.)

Pelvic findings in this group of patients were normal. No gross pelvic pathology was encountered. With exception of one patient who had had a unilateral salpingo-oophorectomy fourteen years before, this group had had no previous gynecological surgery. In three patients the uterus was described as "hard and small." Polycystic ovaries were not found in this group. One patient had a very tight internal os. After dilatation and curettage, and the use of a stem pessary for two months, the patient became pregnant. (The husband in the interval had been treated for prostatitis.) One patient had an annular erosion of the cervix which was treated by electrocautery; two patients had old cervical lacerations which were well healed, and there was no endocervicitis. No other cervical pathology was encountered in this group.

Two of these 35 pregnancies resulted in spontaneous abortion at six and eight weeks. All others were carried to term and resulted in healthy living babies.

Twenty-seven patients showed tubal patency by carbon dioxide insufflation (Rubin). These were checked by a manometer pressure of less than 80 mm. of mercury, together with the occurrence of referred pain in the shoulder after arising. Without the occurrence of shoulder pain no Rubin test was considered as conclusive. In four patients repeated tests failed to reveal the passage of carbon dioxide gas, but x-ray examinations following the injection of iodized oil showed long tortuous tubes of the infantile type, with spill from the fimbriated end of the tubes. These patients were treated with spasmolytic drugs in their preovulatory phase. Pavatrine (beta-diethylaminoethyl fluorine-9-carboxylate hydrochloride) has been used routinely in this study after one negative Rubin test, and the percentage of positive Rubin tests after its use seems rather significant as to its positive value.

All patients had negative blood tests for syphilis; moderate anemia was present in some patients and was treated with iron. Eighteen of the twenty-five patients in whom the basal metabolic rate was determined had a rate ranging from –1 per cent to –18 per cent, with an average of –10.5 per cent. One patient had a basal metabolic rate of 0, four patients had values of +2 to +6 per cent, and only two patients had a rate of +27 per cent and +30 per cent, respectively. All patients with a basal metabolic rate of less than +5 per cent received at least one and one-half grains of thyroid daily.

Six husbands showed sperm counts between 5 and 40 million. Normal morphology and motility were present in these specimens. These couples had been married one, two, six, eight, and ten years, respectively, without the use of contraception. In three other cases pregnancy resulted soon after

severe pyospermia of the husband was brought under control. These couples had been married three, five, and six years, respectively.

Twenty-six of these 35 patients became pregnant in from one to fourteen months after basal body temperature studies and utilization of the fertile period were instituted.

No other therapy was employed. It is felt that observation of the fertile period was an important factor in these patients.

Five patients were found to be in early pregnancy at their first visit. These patients had been married from two to seven years without the use of contraceptives.

Estrogenic preparations, progesterone, and/or occasionally *Synapoidin*, were used. None of the patients who became pregnant were under hormonal therapy at the time the pregnancy occurred or had been under hormonal therapy within three months of that time.

One patient, infertile for five years, was under treatment for 21 months for a hypoplastic genital status. She was given various hormones in addition to estrogenic therapy. This same estrogenic therapy was continued elsewhere for two months. The patient became pregnant but aborted at six weeks.

One patient was studied by vaginal smears and basal body temperatures for six months, and pregnancy did not occur in spite of good evidence of ovulation. A ventral suspension for a fixed retroverted uterus was followed by pregnancy within six weeks after surgery. This patient we delivered of a full-term baby.

Discussion

Several factors become obvious when this group of successfully treated sterile couples is evaluated. The majority of patients had a low-normal or low basal metabolic rate, suggesting once again that lack of thyroid is probably the most important single endocrine factor in sterility. Many of these patients, however, had been on thyroid medication before entering into this study, and, therefore, thyroid alone cannot be credited for the successful outcome. Two-thirds of all patients became pregnant when they observed their fertile periods and were given sex instruction. Postmenstrual sexual abstinence was impressed on these patients, and marital relations were permitted only during the week of the probable ovulation date as calculated for each individual patient after several months of temperature readings had been taken. Only three patients out of a much larger group—still under observation—became pregnant after hormonal therapy other than thyroid. One patient became pregnant after surgery for her fixed retrodisplaced uterus. Eight patients showed many anovulatory cycles mixed with occasionally ovulatory cycles on their charts.

The figures presented from this material show that a thorough study of both partners in every infertile mating pays dividends. Detailed instruction of the patient in the utilization of the fertile period seems to be one of the most important factors in overcoming sterility. What curative effect the performance of a Rubin test may have, cannot be decided. Hormonal therapy with the exception of thyroid does not seem to play any role in the successful treatment of infertility.

Five patients were pregnant at the time of their first visit to the clinic. What psychosomatic factors may play a role in such apparent coincidence cannot be discussed here since psychiatric studies were not carried out. However, it is a well-known fact that previously infertile women will not infrequently seek help for their infertility just at the time when they have become pregnant.

TABLE V. INCOMPLETELY STUDIED GROUP

106 couples			
Average age	30.2 years		
Average number of years married without contraception	6.3		
Previous pregnancies	14 full term		
	14 spont. abortions		
	5 induced abortions		
	1 tubal pregnancy		
Number of physicians consulted previously	None	19	17.9%
	1-3	77	72.6%
	4 or more	10	9.5%

Incompletely Studied Group.—One hundred six patients did not complete their work-up. The average age of the patients, the number of years married, and the number of physicians seen are about the same as in the other groups (Table V). The incidence of secondary sterility is somewhat higher, about 12 per cent. This, as well as nine adoptions which were carried out while under treatment, may account for failure to follow through and return for the necessary visits.

Table VI shows that 77 patients, 72.7 per cent, made between one and three visits to the clinic, and only 29, or 27.3 per cent, returned four to seven times, which in these patients was not sufficient to establish a diagnosis.

TABLE VI. INCOMPLETE WORK-UP

NUMBER OF VISITS TO CLINIC	PATIENTS	
	NO.	%
1-3	77	72.7
4-7	29	27.3
	106	100

The pelvic findings are summarized in Table VII. Semen analysis was carried out in only slightly more than one-half of the patients. The others either refused the examination or never returned.

TABLE VII. INCOMPLETE WORK-UP

	NO.	%
Pelvic Findings.—		
Normal	77	72.6
Hypoplastic status	9	8.5
Cervical erosion	4	3.8
Adnexal mass (pelvic inflammatory disease)	5	4.7
Endometriosis	2	1.9
Ovarian cyst	3	2.9
Prolapse	1	.9
Cervical stenosis	1	.9
Polycystic ovaries	2	1.9
Fibroid uterus	2	1.9
	106	100
Semen Analysis.—		
Normal specimen	36	34.0
Oligospermia	26	24.5
Not examined	44	41.5
	106	100

Table VIII gives the reasons for the failure to complete their work-up. The reason was either evident from notes on the chart or was obtained by follow-up through the Social Service Department.

Follow-up one year after the last visit disclosed that five pregnancies had occurred in this group of patients. Two of these pregnancies followed removal of large ovarian cysts. Neither of them returned for postoperative study. Three other pregnancies occurred spontaneously. One of these five patients had a spontaneous abortion, and the other four were delivered of full-term living babies.

The two peritoneal reactions listed in Table VIII were the only ill effects among all the Rubin tests and Lipiodol studies carried out. Both patients lacked either history or findings of any pelvic inflammatory disease, and their cervices did not show any pathology. One can hardly blame these patients for not returning. If they had, further investigation of tubal patency would have been ill advised.

TABLE VIII. REASONS FOR NOT COMPLETING STUDY

	NO.	%
Left city for residence elsewhere	11	10
Went to another physician and did not return	11	10
Refused cooperation in submitting semen specimen or to have Rubin test	22	20.5
Adoption followed by "lack of further interest"	9	9
"Discouraged" by lack of success	22	20.5
Unable to reach for follow-up	25	24
Peritoneal reaction following Rubin test	2	2
Other reasons:		
Inconvenient hours	2	4
Criticism of clinic care	2	
	106	100

Summary

A study of 240 infertile couples is presented. Of these, 134 couples had completed their studies and were under observation from twelve to eighteen months. Forty-eight and five-tenths per cent were classified as female sterility and 25.4 per cent as male sterility. The pathology in these sterility groups is discussed. Twenty-six and one-tenth per cent achieved pregnancy.

The factors responsible for successful treatment in this series are believed to be: (1) a thorough study; (2) detailed instruction in utilization of the fertile period and improved sex habits; and (3) the judicious use of thyroid extract.

Any "specific" therapy used in the cure of the infertile mating must show a significantly higher percentage of success in order to be recognized as being of therapeutic value.

55 E. WASHINGTON STREET

The author wishes to thank Dr. Ralph A. Reis for the review of the manuscript and Mrs. M. T. Stern for the social service follow-up of the patients.

Discussion

DR. IRVING F. STEIN.—Progress in the study of fertility and sterility has been especially notable in the past thirty years. Prior to this time there were two outstanding books on the subject of sterility, one by Arthur Giles of London and the other by Max Hühner of New York. When Rubin improved upon our previously accepted methods of testing tubal patency, by using gases instead of liquids, he opened wide the gateway to

investigation of the entire field of sterility. The tubal factor became of paramount importance because of Rubin's epochal contribution.

Studies of the male factor had appeared, especially from Boston and New York, but interest in that field lagged until just the past few years, when it has been revived, and valuable additional information has been contributed by Walter Williams, Simmons, Michelson, and many others.

The relationship of ovulation to the menstrual cycle was established, particularly by Hartman, Hertwig and Rock, and others, who identified ovulation with midcycle symptoms and signs and recovered human ova from the Fallopian tubes at laparotomy. Change in the consistency of the cervical mucus is now recognized as a characteristic of ovulation.

Just to enumerate a few other advances which have been made in the past few years: (1) the recording of basal body temperatures and its interpretation; (2) the use of endometrial biopsies on the first day of menstruation; (3) the study of daily vaginal smears, which, when properly interpreted, show the occurrence of ovulation and its relation to menstruation; it may also indicate pregnancy at a very early stage; (4) pregnandiol determinations have been helpful in studying ovulation, pregnancy, and abortion.

After considerable study, the American Association for the Study of Sterility has accepted *minimum standards* for investigation of both male and female partners, incorporating the most practical of these and other tests in an outline. Copies of the minimum standards are available through the secretary of the society, Dr. Walter Williams of Springfield, Mass.

Concerning Dr. Frank's presentation: his report is actually not a study of 240 couples, since he states in his paper that only 134 were investigated fully and followed. Some of the remainder were seen only one to three times; five women were already pregnant when they made their first visit and the remainder were incompletely investigated so that they should not have been included in his statistical compilation.

I would like to ask what minimum standards Dr. Frank adopted for the investigation of infertility. He listed numerous tests which might be performed; some of these he tried and discontinued but he failed to give a complete outline of his routine inquiry. What were his criteria of tubal obstruction? What were the pelvic findings in these patients? What were the associated symptoms and findings? I refer here to stigmata of infection, such as purulent cervicitis, Skene's gland infections, etc. The essayist states that he found only 3 cases of erosion which required cautery treatment. I am sure we all would be interested to know if the cervix was inspected in all cases of infertility and particular notice taken of the cervix in those patients in whom he diagnosed tubal obstruction. It has been our experience that chronic cervicitis with or without erosion occurs in over 50 per cent of sterility patients with a history of pelvic inflammatory disease, abortion, or previous confinement.

Concerning the male factor: again no standard was mentioned by the essayist for routine semen analysis. I would like to ask how many samples of sperm he required and how they were obtained. Were all of his semen specimens obtained by withdrawal after coitus? Were they obtained by masturbation or were some examined by the Sims-Hühner technique—a postcoital test? I would like to know in detail of what the sperm examination consisted. Were *stained* spreads studied for abnormalities? Were counts made in each instance and what reagents were used to facilitate the accuracy of the counts? Were these husbands subjected to complete physical and genital examinations?

When the postcoital test was performed, was survival time of spermatozoa in cervical mucus observed? In this connection, we have in publication the results of a study of sperm survival in cervical mucus during the ovulatory phase of the cycle. We found that whereas spermatozoa survive for but a brief period of hours pre- and postmenstrually, they retain active motility from *two to six days* in the thin, transparent mucus which is characteristic of ovulation. Furthermore, we found, as has Simmons, that among sperms recovered from cervical mucus at this time, only the normal forms retain motility while the deformed and other abnormal forms are immotile. Stained spreads of these samples show that a smaller number of abnormal forms gain entrance to the cervical canal than are found when obtained from the same male partner by ejaculation.

I am very anxious to know what treatment Dr. Frank found to be so successful for males with oligospermia and pyospermia. It has been our experience that when we encountered male partners with either a substandard count (below 60,000,000/c.c.), marked oligospermia, or pyospermia, treatment even in the hands of the most experienced urologists has been extremely disappointing. We do not question Dr. Frank's veracity, but we wonder whether with such successful matings, one should *cherchez l'homme.*

DR. FRANK (Closing).—Dr. Stein is correct in saying that 240 couples were not treated, but they were all studied and the available results seemed of interest to us, and they therefore were all included in the study.

As far as the incidence of cervicitis is concerned, I was amazed myself at the very low rate of cervicitis and cervical erosion in our material. I am sure there are not more than 5 per cent cervical lesions in these nulliparous sterile patients; in private practice the incidence is much higher. But we must not forget that the majority of these patients had been treated for sterility elsewhere, and the important cervical factor had been eliminated there.

As far as semen analysis is concerned, the established values in the recent literature are used as the guide to normal. Details in this respect were omitted, because many excellent outlines for sperm studies are in the literature.

THE EFFECTS OF INTRAVENOUS INJECTIONS OF ERGONOVINE AND SOLUTION OF POSTERIOR PITUITARY EXTRACT ON THE POSTPARTUM PATIENT

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WE HAVE noted that some women who were delivered under low spinal anesthesia (saddle-block), which allows the patient to remain awake, experienced sudden and brief episodes of nausea and vomiting immediately following delivery. As the only drugs given during delivery were intravenous oxytocics at the moment of presentation of the anterior or posterior shoulder, it was thought that the oxytocic drug was responsible for the symptoms. The oxytocics employed in the placental stage, as described by Dieckmann et al.,[1] are ergonovine or 1 unit of solution of posterior pituitary extract, administered intravenously for rapidity and surety of action.

We decided to investigate the systemic effects of the oxytocics on postpartum patients. The literature and pharmacologic textbooks on ergonovine state, with one exception, that there are no systemic effects. There are many reports, however, on the toxic effects of ergot alkaloids on the cockscomb, the cat and dog blood pressure, and the guinea pig and rabbit intestine and uterus, all well defined by Davis and associates.[2] Peripheral gangrene has also occurred with all of the ergot alkaloids except ergonovine.

The untoward reactions of pituitary extract have been fully described. Grimes et al.[3] were the first to state that ergonovine given intravenously occasionally produces cyanosis of chest, neck, head and arms, but is without serious general effect.

Material and Results

In our study, an initial group of 25 postpartum patients were each given doses of 2 ml. (0.4 mg.) ergonovine maleate intravenously and observed for subjective complaints, which could be compared with their stated reaction of sensations experienced during similar dosage at time of delivery. In the accompanying table, the symptoms are grouped anatomically, some patients experiencing two or more of the reactions. Of the 25, 16 could recall no untoward symptoms at time of delivery, but their failure to remember may be attributed to amnesia or anesthesia induced by drugs given during labor. Another 4 patients definitely stated that there had been no reaction at time of delivery. Only 5 patients definitely reported nausea and/or vomiting at time of delivery; none of these experienced nausea or vomiting after the postpartum study dose. There were, however, 4 who experienced nausea after the study dose, one of whom did vomit. The one who vomited and another of the nausea cases were tested subsequently again with an intravenous injection of 2 ml. normal saline; neither experienced nausea or vomiting.

The most usual complaint was that of cramping (15 of the 25 tested). This was described as abdominal, but was found to correspond to the uterine contraction. This pain was more notable in the recent parturient (2 to 5 days); few cramps were reported by the late postpartum patient (6 to 10 days). Dizziness was experienced by 6; while flushing, headache, and cardio- or laryngospasm was noted by equal numbers, namely 3. No reaction at all was reported by 2 patients, while 2 others reported relief from perineal (episiotomy) pain.

The psychic element of an intravenous injection was considered and another series of patients were tested by injections of 2 ml. ergonovine maleate (0.4 mg.), 1 unit solution of postpituitary extract, and 2 ml. of normal saline, on subsequent days. This group of 12 patients was divided in two so that half received the ergonovine medication on the first trial day and half the pituitary medication on the first day, thus reversing the order of administration of the three medications. In both series of patients (25 and 12) studied, neither the patients nor the doctors administering the injections were aware of what solutions were in the syringes at the time of testing.

In the latter control series of 12 patients, increase in blood pressure (10 mm. systolic or diastolic) was noted in 7 patients (58 per cent) receiving ergonovine and 11 patients (92 per cent) receiving pituitary, also in 1 receiving saline. Cramping was experienced by 6 with ergonovine, 9 with pituitary. Flushing was noted by 2 with ergonovine and 2 with pituitary (not the same patients). Dizziness was reported by only 1 patient with ergonovine, but 5 with pituitary; nausea in 1 with ergonovine and in 2 with pituitary (not the same patients). Perspiration and desire to urinate or defecate and cardio- or laryngospasm was felt by one each with pituitary or ergonovine. Headache and tingling of breasts was also reported by one patient each with pituitary. Ergonovine left 4 patients asymptomatic, while pituitary had some effect on all.

Of the 12 patients, an increase (10 mm. systolic or diastolic) in blood pressure was noted in 60 per cent of those receiving ergonovine, 91 per cent of those receiving pituitary solution, and 9 per cent with saline. Pituitary solution also caused bradycardia in 91 per cent and circumoral pallor in 75 per cent.

In combining both series with ergonovine (37 cases), 57 per cent (21 patients) complained of cramping, 5 of flushing, 7 of dizziness, 5 (14 per cent) of nausea (only one vomited), 4 of cardio- or laryngospasm, 3 of headache, 2 of desire to urinate, and one, each, of desire to defecate, of tinnitus, and of palpitation. Only 6 postpartum patients stated that they were free of any symptoms after receiving 2 ml. of ergonovine maleate intravenously.

To illustrate what degree of the study may be shaded by the psychic element of intravenous injection, only one of the second series (12) receiving plain saline expressed any symptoms—desire to micturate and to defecate, associated with audible bowel sounds. But 3 were found to have tachycardia, 2 had bradycardia, and one had increased blood pressure after injection of saline.

Summary

Symptoms associated with one unit of solution of posterior pituitary extract given intravenously occur frequently but are transient, variable, and do not contraindicate the use of the drug. Injections have been given to thousands of patients and only one in over 28 years was found to be unusually susceptible, and while she was sick for several hours, she was never critically ill. She also consented to two subsequent studies. Death is usually due to hemorrhage and shock from the ruptured uterus following the injection of from 5 to 10 units of the pituitary solution.

There are numerous subjective symptoms in postpartum patients receiving oxytocic medication intravenously. In 2 groups of patients totaling 37 who received intravenous injections of ergonovine maleate 0.4 mg., there were 57 per cent who experienced cramping; 19 per cent dizziness; 14 per cent nausea (one case associated with emesis); 14 per cent flushing; and small numbers who complained of cardio- or laryngospasm, headache, desire to defecate or to urinate, tingling of breasts, tinnitus, and palpitation. Very few of the symptoms can be attributed to the psychic effect of an intravenous injection. Also, there were 58 per cent who developed a transient rise in blood pressure after intravenous ergonovine. Thus, one must conclude that a therapeutic dosage of ergonovine given intravenously can produce definite, distressing symptoms which are transient and variable.

TABLE I. SYSTEMIC EFFECTS OF INTRAVENOUS INJECTIONS—PER CENT OF PATIENTS

SYMPTOMS	1ST SERIES	2ND SERIES		
	ERGONOVINE	ERGONOVINE	PITUITRIN	SALINE
1. *Head* (Flushing, dizziness, headache, tinnitus, perspiration)	52	33	75	0
2. *Thorax* (Cardio- or laryngospasm, tingling of breasts, palpitation)	20	9	17	0
3. *Abdominal* (Cramping, desire to defecate or to micturate)	62	67	100	17
4. Nausea and/or vomiting	15	9	17	0
SIGNS				
1. Bradycardia		17	91	17
2. Increased blood pressure		58	91	9
3. Audible bowel sounds		0	50	9
Number of patients	25	12	12	12

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TRASENTINE: EXPERIENCE WITH ITS USE IN OBSTETRICS AND GYNECOLOGY

A Preliminary Report

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THE antispasmodic drug Trasentine* has been used and found effective in the relief of spastic conditions of the gastrointestinal[5] and urinary tracts.[1] Its mode of action of relaxing smooth muscle spasm directly and through parasympathetic depression[2, 4] suggested that it might be of value in obstetrics and gynecology. Kurzrok[3] reported some experience with the use of the drug for dysmenorrhea and transuterine tubal insufflation and was favorably impressed.

I. *Transuterine Fallopian Tube Insufflation.*—Trasentine has been administered in doses of 100 mg. given intramuscularly thirty to sixty minutes before performance of tubal insufflation (Rubin test) with sufficient incidence of success to be encouraging. Five patients were chosen for the use of Trasentine who had had two or more insufflations with pressure of 200 mm. Hg without successful passage of gas through the tubes. Prior to the performance of hysterosalpingography it was elected to try Trasentine to ascertain the possible presence of spastic closure of the tubes. The drug was chosen as an alternate to the use of atrophine. for antispasmodic action. In the cases in which it has been used, the relief of tubal spasm has been accomplished without the undesirable effects usually accompanying atropine administration (flushing and dryness). In the one case where spasm was not demonstrated by relief following Trasentine administration, subsequent salpingography revealed organic tubal occlusion.

II. *Dysmenorrhea.*—Trasentine was tried on 25 women who had severe, intractable dysmenorrhea with no organic pathology palpable or demonstrable. In several of these cases test suppression of ovulation by the use of oral estrogens in the first half of the cycle had failed to relieve the dysmenorrhea. Trasentine was administered both intramuscularly and orally.

Intramuscularly, Trasentine, 100 mg. (2 ampoules), was given as a single dose. This dose gave complete relief or, at least, 75 per cent relief in thirty to forty-five minutes. All women were sufficiently relieved to be able to continue working at their usual occupation. Ordinarily, following the usual remedies for dysmenorrhea, these women had had to go home to bed.

Orally, 150 mg. (2 tablets) were given at the first sign of dysmenorrhea and repeated at two- to four-hour intervals to control the discomfort, allowing up to 4 doses a day (600 mg.). Most patients reported complete relief after one or two doses, but all patients reported some relief. All patients were impressed with the degree of relief and the absence of the side effects usually felt from taking ordinary remedies, i.e., sleepiness, dizziness, and nausea. It was

*Trasentine is the hydrochloride of diphenylacetyldiethylaminoethanol (Ciba).

found that, regardless of the manner of administration, better relief was afforded, and more promptly, if the medication was given before the peak of the pain was reached. In the few cases in which the drug was given to women in severe pain, the results were not nearly as satisfactory and were slower in being accomplished. Comparatively, the intramuscular has been more effective (quicker and more efficient) than the oral route.

III. *Obstetrics.*—For some years we have been administering oral antispasmodics to aid in relaxing a cervix dilating poorly in the first stage of labor. Often, with a good uterine mechanism and a cervix that had remained static at 2 to 3 cm. dilatation for several hours, oral administration of comparatively large doses of antispasmodic medication (Trasentine 450 mg., or Pavatrine 750 mg., or Syntropan 700 mg.) resulted in dramatic dilatation of the cervix in one or two hours. However, the oral administration of tablets has always been unsatisfactory. There is often difficulty in swallowing or retaining the tablets, and always uncertainty as to the efficacy of absorption.

Therefore, intramuscular Trasentine has been used in 100 mg. doses. The drug has been used to the present for those patients whose progress in cervical dilatation had become static for two to six hours. Without altering any other existing condition, i.e., no change of sedation, neither addition nor withdrawal of Pitocin being given to accelerate the labor mechanism, the Trasentine has been given and usually within thirty to ninety minutes a very dramatic improvement in cervical dilatation has been noted. The change in dilatation of the cervix has been most impressive and attributable only to the addition of the Trasentine to the labor picture, which was allowed to continue unaltered in all other respects. In each case the cervix had remained static for a sufficient number of hours to make it unlikely that the noted effect was merely the culmination of labor and time. In most of the 23 cases observed to the present the change has been sharp and definite.

Comment

At present no great number of cases are being offered to substantiate the impressions here noted. A series of cases of substantial magnitude is in the process of being collected. More precise results will be offered as soon as available. We have been impressed by the experiences that we have had to date and are continuing the work.

Trasentine has been completely innocuous in the doses and manner of administration thus far used. No side effects have been encountered except a very transient dizziness and slight transient hypotension which followed the use of 50 mg. Trasentine intravenously, used in a few cases, early in our experience.

The rationale for the use of Trasentine for dysmenorrhea is directly related to the in vitro work showing reduction of uterine spasm induced by oxytocics and inhibition of spasm which was induced by sympathetic nerve stimulation,[2] following the administration of Trasentine. Thus, it might be construed to act in part as a "medical" presacral neurectomy.

The use of Trasentine in tubal insufflation was rational following the demonstration of the "atropine-like" effects of the drug without the unpleasant atropine side effects.

The use of Trasentine to aid cervical dilatation in labor was based on our experience with the effect of the inhibition of sacral nerve impulses on the cervix. Labor and delivery in our patients are managed predominantly under continuous caudal analgesia (about 88 per cent). We had noted that very rapid dilatation of the cervix often occurred within the first hour of caudal analgesia. Thus, removal of the parasympathetic effects on the cervix by block-

ing the sacral nerve roots seemed to permit rapid dilatation of the cervix. The Trasentine, which acts by parasympathetic depression and smooth muscle relaxation, has a "caudal-like" effect on the cervix and has proved itself worth while.

Summary

A preliminary report has been offered of experience with Trasentine (1) to relieve dysmenorrhea, (2) to relax Fallopian tube spasm, (3) to aid cervical dilatation in the first stage of labor. Significant statistical numbers of cases are being collected and the aggregate results will be analyzed and presented, when available.

Acknowledgment is made to the Ciba Pharmaceutical Products, Incorporated, who supplied the Trasentine for this study.

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ESTROGEN THERAPY BY IMPLANTATION OF ESTRADIOL CRYSTALS

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IN PREVIOUS publications[1-3] estrogen therapy of various gynecologic conditions by intramuscular injection of oil solutions and by mouth was described in relation to effects on vaginal smears. The purpose here is to present comparative results from intramuscular administration of an aqueous suspension of estradiol crystals.* Following injection of such a preparation, the aqueous menstruum is promptly absorbed, leaving the pure hormone deposited in the muscle in the form of minute crystals with enormous surface area from which hormone absorption is prompt and uniform, closely simulating the physiologic release of estrogen from the normal ovary.

Deanesly and Parkes[4-6] first used implantation of crystals and compressed pellets of pure hormones and showed it to be the most efficient mode of administration. Subsequent investigators, particularly Geist, Walter, and Salmon,[7-12] showed absorption to be more uniform from loose crystals than from a sizable compressed pellet, due to the formation about the pellet of a thick avascular capsule more or less impermeable to the hormone. The crystals, on the other hand, became surrounded by less dense tissue in the form of tiny nodules through which absorption of the hormones progressed at a more uniform rate. Moreover, the greatly increased surface area of the crystals gives much more rapid absorption, making the implantation of crystals particularly adaptable to treatment of the more profound estrogen deficiencies.

Three criteria were used by Geist, Walter, and Salmon, and again in the present study, for comparing crystalline implantation therapy with injection of intramuscular oil solutions and ingestion of oral preparations: (1) effects on the vaginal smear, (2) persistence of pituitary inhibition in control of climacteric symptoms, and (3) persistence of clinical improvement in other estrogen deficiencies. The vaginal smear is well recognized as a true index of the effectiveness of estrogen therapy.[13] Previously reported studies[1] have demonstrated estrogen therapy to be effective when there is concomitant change of an atrophic smear to one of complete cornification. This criterion eliminates all possibility of subjective complications. The cases reported here were studied from these standpoints. The series reported by Geist, Walter, and Salmon, in which intramuscular implantation of loose crystals of estradiol was used, demonstrated this method of therapy to be safe and efficient in estrogen deficiency resulting from surgical or roentgen castration or natural menopause. These investigators recommended this method as a prophylactic procedure at the time of bilateral ovariectomy.

Material

For the past year and a half, 40 patients with marked forms of estrogen deficiency have been treated by this method in comparison with intramuscular injection of oil solutions and with oral therapy. After adequate experience in the use of any one form of estrogen therapy as it affects the vaginal smear, definite and fairly accurate impressions may be gained concerning comparative efficacy of another form of estrogen therapy. Long experience with the effects

*Micropellets Progynon used in this study were supplied in part by the Schering Corporation, Bloomfield, New Jersey.

of intramuscular oil solutions and oral estrogen preparations on the vaginal smear in a variety of estrogen deficiencies has made possible an estimate of the comparative efficacy of aqueous suspension of estradiol. One milligram of estradiol in microcrystalline form gives an effect on the vaginal smear equal to that from 12,000 rat units of estradiol benzoate in oil intramuscularly.

The 40 patients included in this study varied in age from 38 to 63 years. Of these, 75 per cent had been under hormone therapy previously, either injections in oil or tablets orally. In 55 per cent of the patients the menopausal symptoms, hot flushes, nervousness, insomnia, fatigability, and mood changes were severe. In 50 per cent menses were absent and in the remainder irregular. Vaginal smears were made on all patients before and after micropellet implantation. Before therapy 50 per cent of the vaginal smears were of menopausal type, 37 per cent were of ovarian insufficiency type, and the remainder were under the influence of previous estrogen therapy. Hysterectomies had been performed in 42 per cent, other pelvic operations in 17 per cent, and the remainder had had no surgery. Breast sensitivity under therapy was complained of by 32 per cent. In no case was this severe. Three patients who complained of this symptom had had it more severely under previous therapy.

Dosage varied from 0.5 to 2.0 mg. by injection once weekly. The average dose was 1.0 mg. once weekly. The vaginal smear response to therapy was 10 to 20 per cent cornification. At this level good clinical response was obtained. Vaginal smear was shown to be a true index of estrogenic effect. In 11 of these 40 cases response was excellent, in 18 good, and in the remainder fair. All were benefited.

Detailed case histories of two patients are given to illustrate further the results of this form of therapy:

D. D., aged 47 years, housewife with two grown children. First seen June 8, 1949. Hysterectomy in 1940. One ovary left in situ. Had been taking Conestron 1.25 mg. daily by mouth for months. Severe hot flushes worse at night. Insomnia. Extremely tense and nervous, cried easily, depressed, periods of exhaustion not related to effort. Following thyroidectomy for nontoxic adenoma two years previously, she was taking 1 grain thyroid daily with a basal metabolic rate of –16. Physical examination negative except for blood pressure of 178/84. Vaginal smear showed ovarian deficiency type with 10 per cent cornified cells. This cornification was a result of her oral estrogen therapy. She was given 5,000 R. U. Progynon-B intramuscularly three times weekly for two weeks, resulting in a vaginal smear showing full replacement by cornified cells. This therapy was then replaced by Micropellets Progynon, 1 mg., once weekly. This was increased to 1.5 mg. when the vaginal smear response dropped, and her nervous symptoms returned. On this dosage she is showing 20 per cent cornification in her smear and her symptoms are well controlled. She has no flushes, is sleeping well, is no longer nervous, and has returned to her previous program of activities. Blood pressure varies from 162 to 172/94.

M. J., aged 42 years, housewife with one child of 11 years. First seen February 1, 1949, with history of heavier but regular menses for past year. Severe nervousness and spells of exhaustion, worse in last days of menstrual cycle. A few hot flushes. Poor sleeper and in general showed a mild anxiety state. No pelvic operations. Physical examination normal except for dry skin and hair. Uterus retroverted. Blood pressure, normal. Vaginal smear of ovarian insufficiency type. She was given 1 mg. Micropellets Progynon intramuscularly once weekly between menses. Excellent response to this therapy. Menses less heavy, sleeping better, has more energy, and is much more stable in every way. Vaginal smears show 10 to 75 per cent cornification, depending upon time in cycle smear was taken.

Comment

Constant search is made for optimal method of estrogen therapy from the standpoints of simplicity and efficacy. Under properly controlled conditions

equivalent results can be obtained from oral or parenteral therapy. Oral therapy has certain disadvantages, particularly in the patient not under continuous observation. It is impossible to be certain that oral or written directions will be followed. Estrogens may be continued for too long a period and advised rest intervals may be ignored. Absorption and partial destruction in the liver make dosage difficult to evaluate. Liver function may be impaired and permit estrogen to accumulate to overdosage levels. Symptoms of overdosage include breast congestion, which may be evidenced as swelling, erection and tenderness of the nipple, leucorrhea, pelvic congestion with sensation of menstruation even in absence of the uterus, weight gain, headache, tension in trapezius, and overstimulation and restlessness at night. The parenteral route gives better patient control and dosage regulation. Menopausal symptoms of nervous origin are more easily controlled since absorption is more uniform, simulating normal ovarian estrogen production, maintaining a steady level without fluctuations. In addition a certain amount of psychotherapeutic effect results from the injections. In Micropellets Progynon we have a preparation which causes no local reaction or irritation. Breast stimulation and leucorrhea occur infrequently. Effect of injection lasts seven to ten days. Symptoms are controlled when the average vaginal smear shows 20 per cent cornification.

In this group of 40 patients 28 per cent showed excellent response, 45 per cent a good result, and 27 per cent a fair response to injections of Micropellets Progynon in weekly dosage of 0.5 mg. to 2.0 mg. In the 11 patients showing only fair response, 7 were definitely psychoneurotic or had severe anxiety states, one had an agitated depression and refused shock therapy after one treatment, one had alcoholic cirrhosis and died of acute hepatitis, one had severe hypertrophic osteoarthritis and one undulant fever.

Salmon, Geist, and Walter[8] used injections of 5 to 30 mg. crystals. Using this larger dose they encountered hyperplasia of the endometrium lasting up to three and one-half months. There was marked effect on the breasts, which showed fullness, swelling, redness and tenderness of the nipples by the end of the second or third week. Moderate uterine bleeding for from several days to several weeks was another complication from this high dosage. Uterine bleeding occurred in 65 per cent of the patients implanted with 25 to 30 mg. crystals. No prolonged or excessive bleeding occurred in any patients in this series in which we used a dosage of 1 mg. Micropellets.

Summary and Conclusions

A crystalline estradiol preparation, Micropellets Progynon, was given intramuscularly to a group of 40 patients between the ages of 38 and 63 years who showed symptoms of ovarian deficiency or of the menopause. All of these patients responded favorably to this therapy, while 75 per cent showed good to excellent results with weekly injections of 0.5 to 2 mg. (average 1 mg.). Vaginal smear and clinical improvement were the criteria of estrogenic effect. Vaginal smear response averaged 10 to 20 per cent replacement with cornified cells. Greater estrogenic effect was required only in an occasional case.

There were no local signs of irritation at site of injection. Effect on breasts was minimal, as were other phenomena of overdosage. The fluctuation of hormone level, which occurs with the use of oily injections given irregularly or twice weekly, is replaced, when crystalline estrogen is implanted, by a steadily maintained level with much greater relief of the deficiency symptoms.

After 15 years' experience in practice, Micropellets Progynon was found to be the most satisfactory estrogen preparation. It is more prompt and pro-

longed in action than intramuscular injections of oil solutions and oral preparations. This aqueous suspension of estradiol is the preparation of choice from the standpoints of estrogenic activity, convenience to patients and physician, prompt and prolonged action, and economy.

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DIAGNOSTIC CULDOSCOPY*

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CULDOSCOPY is a procedure for the visualization of the pelvic organs by means of an optical instrument introduced through the posterior fornix. It is a relatively recent development, in a fifty-year search for a technique that would permit a view of the pelvic organs without subjecting the patient to a laparotomy.

The peritoneoscope had many advocates who ascribed definite advantages to its use in the diagnosis of intra-abdominal conditions, but in gynecology it has a limited field of usefulness. The instrument entered the abdominal cavity at a considerable distance from the pelvic viscera and the tip of the instrument often had to pass through many loops of small intestine to reach the pelvic organs, and not infrequently adhesions made the procedure hazardous or impossible.

In 1940, Te Linde[1] attempted to visualize the pelvic viscera with the peritoneoscope introduced through the posterior vaginal fornix with the patient in the lithotomy position. Air was introduced by means of a bulb, as in the ordinary transabdominal peritoneoscopy. It was found impossible to retain enough air in the peritoneal cavity to prevent the intestines from interfering with visualization of the pelvic viscera.

In 1944, Decker,[4-6] in an effort to improve the use of the peritoneoscope in pelvic diagnosis, adopted the vaginal route to view the pelvic organs—as had been suggested four years before by Te Linde—but with one important difference, namely, that of having the examination in the knee-chest position. It was Decker who realized that a pneumoperitoneum effective enough to keep the loops of bowel out of the pelvis can be produced by utilizing the negative intra-abdominal pressure created by assuming the knee-chest posture. The amount of air entering the abdomen may measure from 800 to 1,500 c.c.

The patient is placed in the knee-chest position. If the culdoscopic examination is to be made with the patient awake, as most of our cases were, she can then maintain the position unsupported for thirty or forty-five minutes, more than long enough to complete the examination by a number of observers. If the patient is given general anesthesia, she can be held in the knee-chest position by having a nurse or intern stand on either side of her with the adjacent arm encircling the patient's thigh. This requires almost no effort. Unless we plan a dilatation and curettage or a possible laparotomy, the patient is not shaved and the vaginal preparation is of the simplest—we use a nonirritating antiseptic solution to swab out the vaginal tract. We do not prepare the vulva, the buttocks or the anal region.

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We have culdoscoped most of our patients under local anesthesia by injecting about 5 c.c. of a 1 per cent procaine solution into the posterior vaginal fornix at the site of the puncture, which is the point of greatest concavity. For general anesthesia we have used intravenous Pentothal Sodium, usually given through a vein in the dorsum of the hand. Caudal as well as spinal anesthesia have also been used successfully. We have also culdoscoped a number of patients with only some preoperative medication. The type and amount of anesthesia must be adjusted to the patient's psyche. Recently we have used 100 mg. of Demerol intravenously preceding the injection of the local. This has enabled us to use local even in the most apprehensive patients.

Having the patient in the knee-chest position, the perineum is elevated by a Sims' speculum. A tenaculum is placed on the posterior cervical lip and the trocar is directed to the point in the vaginal vault where the concavity is greatest. A sudden quick puncture easily perforates the posterior fornix. The wall of this fornix is very thin, consisting only of the vaginal wall, a thin layer of endopelvic fascia, and peritoneum.

Successful puncture of the cul-de-sac is proved by the sound of inrushing air on removing the trocar; the cannula is left in place. The sterile culdoscope is then introduced through the cannula.

The ovaries and the posterior surface of the uterus come into view very readily. The complete visualization of the normal tubes is not always as readily demonstrable. The cervix can be manipulated to bring the anterior surface of the uterus into view and if the bladder is partially distended it, too, can be seen.

At this point in the examination one can resort to another diagnostic procedure, namely, the dye test for tubal patency. Our experience with this step in the culdoscopic examination has not been too satisfactory, perhaps because of lack of sufficient experience, but of the few sterility cases in which we tried it and thought the tubes closed—two patients proved us wrong by promptly becoming pregnant.

When the examination is completed, the culdoscope is removed and the cannula left in place, and the patient lies on her abdomen permitting the abdominal air to be expelled. At this point, making pressure on the patient's abdominal wall will help in expelling some of the retained air. The cannula is then removed. The wound in the cul-de-sac is not sutured. I know of only one instance where the patient returned to her doctor ten days after culdoscopy because of bleeding at the site of the puncture and two sutures were taken to control the bleeding.

The amount of posteuldoscopy discomfort varies directly with how completely the abdominal air is expelled. It varies from none to moderately severe discomfort for a day or two. The usual complaint is of a slight general muscle soreness and/or some shoulder pain.

The indications for culdoscopy are many and fall into several clear-cut groups. Foremost, of course, are those cases in which the history and/or pelvic findings suggest tubal pregnancy. Te Linde points out that an ectopic pregnancy is more often diagnosed as well as overlooked than any other pelvic disturbance and that, fearing the results of failure of the diagnosis of tubal pregnancy, many patients are subjected to a pelvic laparotomy only to find no abnormality or a minor lesion for which surgery was not necessary. Unfortunately, most of the ectopics seem to fall far short of the textbook type where the diagnosis is simple. Of the 96 cases on which this report is based (Table I), in 25 the history and pelvic findings were so suggestive of ectopic that an attempt at an absolute diagnosis had to be made. In only 10 of these patients was the diagnosis of ectopic substantiated by the culdoscope. The remainder of our cases

proved to be salpingitis or some ovarian pathology. No case in which ectopic pregnancy was excluded by the culdoscope was ever found to have it by subsequent observation or operation. In no instance where the culdoscopy indicated a tubal pregnancy did it prove otherwise. I might cite a few of our cases to illustrate this point:

CASE 1.—Mrs. D. H., aged 35 years, para ii, gravida ii, whose younger child was two and a half years of age, was admitted to the Henrotin Hospital on June 24, 1948, with the complaint of pain in the lower abdomen of one day's duration. The patient stated she was well until the day before admission, at which time her menstrual period, which was

TABLE I. DISTRIBUTION OF THE 96 CULDOSCOPY CASES

Ectopic	25
Sterility	13
Amenorrhea	3
Menometrorrhagia	25
Endometriosis	2
Dysmenorrhea	5
Uterine anomaly	1
Pelvic inflammatory disease	2
Adnexal mass	15
Unexplained pelvic pain	5
	96

one week late, started with some spotting. At this time she began to develop some lower abdominal cramps which became so severe that she called a physician who diagnosed a possible acute appendicitis. Her temperature on admission was 100° F. The general physical examination was essentially negative except for some abdominal tenderness over McBurney's point. Pelvic examination disclosed a tender boggy mass in the right lower quadrant, a uterus slightly enlarged and soft, while the adnexa on the left seemed negative. The impression was that of a possible ectopic pregnancy but it was felt advisable to keep the patient under observation. The next day the temperature was normal but the patient complained of more right lower quadrant pain. On June 26, 1948, about thirty-six hours after admission, the patient was culdoscoped. The findings were of a slightly enlarged uterus, the right tube was extremely thickened and markedly inflamed and plastered against the right ovary. The left tube was about three times normal size and also markedly injected with a slight exudate on the surface. The ovaries seemed normal. A diagnosis of acute bilateral salpingitis was made and the patient returned to bed and was placed on antibiotic therapy and discharged as improved on July 13. When seen at the office two months later, the mass on the right had undergone complete resolution and the patient was symptom-free.

CASE 2.—Mrs. N. M., aged 26 years, para 0, gravida 0, entered the hospital July 29, 1948, with a history of continual vaginal bleeding since July 5, 1948, with two episodes of suprapubic pain associated with increase in flow. No urinary or bowel symptoms were present. The patient had expected her menstrual period at about July 2, at which time she spotted and the regular period began three days later. A gynecologist believed the patient had a small right ovarian cyst. The next morning, on July 30, 1948, the patient was culdoscoped and a small right ovarian cyst was seen, but the right tube seemed abnormally thick and there was evidence of clotted blood plastering the tube against the ovary. With a diagnosis of ectopic pregnancy, a laparotomy was performed and a right tubal pregnancy was found. A right salpingectomy and a resection of the right ovarian cyst was performed. The patient made an uneventful recovery.

CASE 3.—Mrs. E. G., a well-developed, well-nourished woman, aged 24 years, para 0, gravida 0, was admitted to the Henrotin Hospital, Sept. 9, 1948, because of a history of

bleeding for the past twelve days and some slight lower abdominal discomfort. Her past medical history was negative. She had had an appendectomy twelve years before. Menstrual history began at about 12 years of age, intervals every two to three months prior to thyroid administration (basal metabolic rate—20). During the last year the menses had been every six weeks and regular. Her last menstrual period on Aug. 19, 1948, came at the expected time. The general physical examination was essentially negative. The pelvic examination revealed a normal-sized uterus, cervix firm and smooth. The adnexa seemed negative except for an indefinite left cystic mass, vaguely outlined and tender on pressure. With these rather indefinite findings and history a dilatation and curettage and culdoscopy were done. The curettage findings were those of a polypoid endometrium and so later reported by the pathologist. Culdoscopy revealed a small right ovarian cyst. In the region of the left adnexa was seen a terminally thickened tube with some blood clots partially extruding from the fimbriated end. A diagnosis of ectopic gestation was made, and a laparotomy was performed. An early unruptured left tubal pregnancy was found, with only a few bits of clotted blood in the pelvic cavity. The right ovarian cyst was resected and a partial left salpingectomy followed by a cuff salpingostomy performed. The patient made an uneventful recovery. This patient has since achieved a normal intrauterine pregnancy, and was delivered on Dec. 20, 1949, of a normal 7-pound male infant.

CASE 4.—Mrs. J. M. was a well-developed but poorly nourished female, 23 years of age, para 0, gravida 0, who entered the hospital on Sept. 23, 1948, with the complaint of a two months' amenorrhea and irregular dull pain in the right lower quadrant, nausea without vomiting in the morning not constant; no fever, no genitourinary symptoms. Onset of menses occurred at 11 years, every 23 days, five days' duration and no pain. Past medical and surgical histories negative. General physical examination negative. Pelvic examination revealed a uterus slightly enlarged, good position, freely movable. The adnexa on the left was negative. In the region of the right adnexa an indefinite small cystic mass was found. It was this finding which was probably the basis of the diagnosis of an ectopic pregnancy with which the patient had entered the hospital. The next morning a dilatation and curettage and culdoscopy were performed. The culdoscope visualized on the right an enlarged polycystic ovary with the tube somewhat thickened and reddened. The ovary on the left was normal but the tube was also thickened, reddened, and the fimbria seemed closed. The methylene blue dye test was performed and no dye was seen to escape from the fimbriated ends of the tubes. The patient ran a low-grade fever for two days, was placed on antibiotics and was discharged afebrile and symptom-free three days after admission.

It is obvious that not in every case would laparotomy have been absolutely necessary to rule out tubal pregnancy with certainty. In some instances simple observation in the hospital would have eventually ruled it out. However, as a result of culdoscopy some of our patients were discharged promptly and with a feeling of safety. In those cases where ectopic gestation was found, the patients were operated on before they sustained any significant blood loss, which made more conservative surgery possible. Te Linde points out that it has been claimed that curettage, pregnancy tests, and especially colpotomy can definitely establish the correct diagnosis. However, all of these steps carry varying percentages of error, while the culdoscope had none. In a recent case on this service, the examiner was misled by colpocentesis to interpret a small amount of blood in the cul-de-sac as indicating tubal pregnancy, when the bleeding actually arose from a corpus luteum, and the bleeding had subsided by the time the laparotomy was performed. With the aid of the culdoscope such a satisfactory view of the ovaries and tubes can be obtained in most cases that the exact origin of the bleeding probably could have been detected and a correct decision for or against surgery properly made.

The following case report illustrates another large category in which culdoscopic examination seems to be specifically indicated.

CASE 5.—Mrs. S. W., a 25-year-old white woman, para 0, gravida 0, had been a sterility problem for the past three years. The entire sterility work-up including that of her husband had been completely negative. Her only additional complaint was that of severe dysmenorrhea. On July 29, 1948, she was admitted into the Henrotin Hospital for culdoscopy. This examination revealed on the surface of both ovaries multiple blue-black nodules along with some follicular cysts. The uterus seemed a little enlarged while the tubes seemed normal. A diagnosis of endometriosis was made and the patient dismissed the next day. On Sept. 12, 1948, the patient was readmitted to the hospital and a laparotomy was performed. At this time the findings were identical with those seen at the time of culdoscopy. Resection of the endometrial implants was carried out. The patient was discharged on the seventh postoperative day in good condition.

This case illustrates the value of culdoscopy in the study of some sterility problems as well as in instances of unexplained pelvic pain and severe dysmenorrhea. In endometriosis early conservative surgery may permit of an eventual pregnancy, whereas delaying the diagnosis might make conservative surgery almost impossible.

The largest number of our culdoscopy cases were in the group of menstrual disorders, mostly instances of functional uterine bleeding. Since most of the patients in this group were scheduled primarily for a dilatation and curettage, we felt we ought to avail ourselves of the opportunity offered and culdoscope all of these patients. In at least 90 per cent of these patients with a history of menometrorrhagia we found a hyperplastic endometrium and bilateral polycystic ovaries. However, in three patients who originally were thought to fall into this group of functional uterine bleeding we discovered three very early unruptured and unsuspected tubal pregnancies. In culdoscoping several patients with a history of primary amenorrhea we discovered two cases of ovarian agenesis. One of these patients with primary amenorrhea occurred in a 19-year-old girl who had been treated for years with various gonadotrophic preparations.

Three of the patients in this group of functional uterine bleeding, in whom the basal temperature record and endometrial biopsy were inconclusive as to whether the patients were ovulating, were found on culdoscopic examination to have a well-defined corpus luteum.

Another important field in which culdoscopy can prove helpful is in the patient who has a small ovarian cyst. One would dislike to subject a patient to surgery and find only a moderate-sized simple follicular cyst that would probably ultimately disappear spontaneously, but oppositely it would be deplorable to permit a small neoplastic cyst to remain in the pelvis with ultimate serious consequences. Ordinarily watchful waiting and disappearance of the cyst will answer the question in most cases, but occasionally ovarian enlargement persists even when it is not due to a neoplasm. The differentiation can frequently be made with the aid of the culdoscope. We found that in almost every patient we culdoscoped, the ovaries could be studied in great detail.

All patients but one whom we have examined thus far have been admitted to the hospital overnight. This one patient left the hospital two hours after the culdoscopic examination and when seen later said she had felt no ill effects.

Our experience with the culdoscope in these 96 cases has convinced us that this procedure is an asset in the study of many pelvic disorders. The information gained in most instances was so detailed and clear concerning the pelvic structures, that such knowledge is not obtainable by any other means except laparotomy.

The only contraindication we have found to culdoscopy is a fixed mass in the cul-de-sac. In the last 60 cases we have avoided culdoscoping any patient with marked adhesions fixing the pelvic structures posteriorly, and as a result we have entered the cul-de-sac readily in every one of these last 60 patients. To date, we have not punctured a viscus and have had no mortality and no serious complications. We feel culdoscopy is a safe and valuable procedure for visualization of the pelvic organs.

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ENDOMETRIAL BIOPSY

Comparison of Aspiration Curettage With Conventional Dilatation and Curettage

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RECENT literature has attacked the delay period in the diagnosis of uterine carcinoma. Howson and Montgomery[1] have found that 76.5 per cent of a total of 259 cases of fundus carcinoma showed delay in diagnosis and beginning treatment. They further state that in 28.5 per cent of these 259 cases the delay is the fault of the attending physician. The average period of delay attributed to the physician was 13.7 months! Forty-eight per cent of the delays attributed to the physician were because no pelvic examination was made.

It is generally accepted that any symptom suggestive of carcinoma of fundus, such as bleeding, discharge, etc., must be thoroughly investigated, especially before any medication is given to control these symptoms. Undoubtedly some of the doctors responsible for the delay in the above-described cases, as well as others, would have more thoroughly investigated the presenting symptom if such investigation did not require hospitalization and anesthesia for diagnosis. Also, undoubtedly, some patients refused investigation because of fear of surgery and finances involved. The patient with but one episode of spotting is especially likely to decline hospitalization for further investigation.

We became interested in evaluating the accuracy of aspiration curettage in an effort to attack the delay period. Since the delay period is due to many factors, such as hospital expense, anesthesia, crowded hospital facilities, patient's fears, etc., we feel that an office procedure would eliminate some of these causes for delay.

Aspirated specimens from the uterus have been used for various studies for many years, probably first advocated by Howard Kelly over thirty years ago. Various investigators have used many methods of obtaining endometrial biopsies. Klingler and Burch[2] recommended a flexible copper tube perforated at the end and attached to a suction apparatus to obtain specimens from the endometrium. In 1935 Randall[3] recommended a rigid hollow tube with a scraping surface for obtaining endometrial specimens for endocrine studies. Novak,[4] in 1935, recommended a somewhat similar tube, together with constant suction, to obtain specimens for similar studies. All of the above concluded that their instruments were satisfactory for obtaining specimens for various endocrine studies but not for diagnosis of endometrial malignancy. Various other authors have commented on the efficiency of this method, but none have made comparative studies between aspiration and conventional curettage in diagnosing malignancy. Williams and Stewart[5] have reported a

group of cases where aspirated, not curetted, material obtained was compared with material obtained by conventional dilatation and curettage.

Material and Procedure

At Roswell Park Memorial Institute, prior to 1946, aspiration curettage was used infrequently and this method was not considered reliable. Since 1946, because of crowded hospital facilities and a long waiting period prior to admission for diagnostic dilatation and curettage, aspiration curettage has been used with increasing frequency. The increasing number of diagnoses of malignancy made from aspirated curetted endometrial material has led to this comparative study.

During this period 301 patients have had both aspiration curettage and conventional dilatation and curettage. Table I presents these cases grouped according to malignant and nonmalignant conditions and also grouped according to agreement or disagreement of the two diagnostic methods. It will be noted from this table that in 95 malignant cases, the diagnostic accuracy of the aspiration curettage equalled the convention method. In the 206 nonmalignant cases, a diagnosis was made from the conventional specimen in a slightly higher percentage (5 per cent) of cases than the aspiration curettage.

TABLE I. FUNDUS CARCINOMA. UTERINE CURETTAGE. ASPIRATION VS. CONVENTIONAL

Total cases	301			
Agreement	257		85.5%	
	NONMALIGNANT		MALIGNANT	
Total cases	206		95	
Agreement	182	88.2%	75	79.0%
Disagreement	24	11.8%	20*	21.0%
	Disagreement			
Aspiration	8 positive		11 positive	
Conventional	16 positive		9 positive	
	Accuracy			
Aspiration		91.2%		90.5%
Conventional		96.0%		88.5%

*In 19 cases the aspiration preceded the conventional.

In the nonmalignant group of the 24 cases which are reported in disagreement, 17 were so reported because of an unsatisfactory specimen obtained by one of the methods. In 11 cases, the aspirated specimen was unsatisfactory and in 6 cases the conventional specimen was unsatisfactory. These unsatisfactory specimens were reported as "blood and mucus only." Thus in only 7 cases where a sufficient amount of material was obtained, was there any disagreement.

Equipment

Very few patients are unsuitable for aspiration curettage. The extremely apprehensive patient for whom anesthesia is almost always required, is a rare problem, as well as patients with cervical canal atresia or intact hymen. The problems of uterine malposition, such as extreme anteversion or flexion and extreme retroversion or flexion, have been overcome by the addition of curettes having different degrees of curvature. The scraping surfaces of the curette have also been altered to include convex and concave scraping bits, as illustrated. Some of these instruments do not appear in any surgical catalogue and have been made in our shop. They are neither difficult nor expensive to

make. With the variety of instruments, as shown, we feel that we can obtain an endometrial specimen from any portion of the cavity.

Method

Numerous authors have advised strict asepsis with preparation of vagina and cervix with strong antiseptics. We do not use strong chemicals. The cervix is cleansed mechanically with a cotton ball. The uterine cavity is carefully sounded to determine its depth, direction, and contour. The aspiration curette or curettes that conform to the curvature as determined are then selected and introduced. The curette is attached to a Luer lok syringe with three finger rings, as illustrated, which allows application of suction as well as curettage with one hand. It is not intended to removed the entire endometrium; however, material is obtained from all portions of the uterine cavity including the horns. Under continuous suction, the specimen is obtained, the curette is removed, and the specimen is washed in 10 per cent formalin. Reinsertion of the curette is usually done to pick up any loose fragments remaining in the cavum, or in cases of extreme malposition the curette with the scraping surface on the opposite side of the curve is substituted, thus permitting curettage of all parts of the endometrial surface.

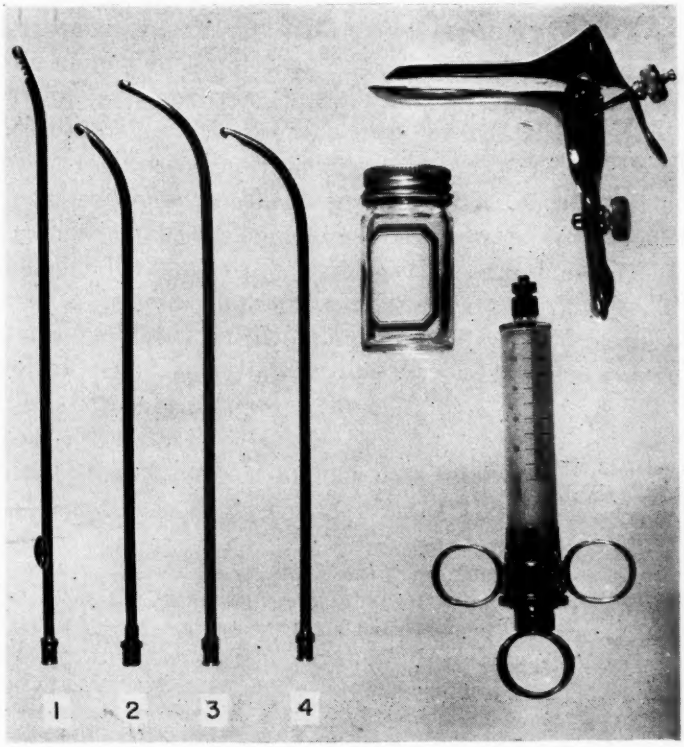

Fig. 1.—*1*, Novak Curette—used endocervically only. *2*, Moderate curve, anterior bite. *3*, Full curve posterior bite. *4*, Full curve, anterior bite. (*3* and *4* do not appear in surgical catalogues. Made in our shop. Used in extreme anteflexions or retroflexions.)

In this group of cases where conventional dilatation and curettage followed aspiration curettage by as much as 40 days, there were no cases showing endometrial infection or pyometria.

We have had no uterine perforations, and have never encountered excessive postaspiration hemorrhage.

Conclusions

1. We find aspiration curettage an entirely safe office procedure and applicable to almost all patients examined.

2. Despite the unanimous opinion of the authors quoted, that aspiration curettage was not satisfactory in the diagnosis of endometrial malignancy, we have found the diagnostic accuracy of this method equal to that of the conventional dilatation and curettage.

3. We wish to emphasize that a single negative specimen by either method should never be considered adequate. A repeat examination by one or both methods is imperative if the symptoms suggest the possibility of malignancy and especially if such symptoms persist. We have had several cases where 3, 4, or 5 conventional curettages produced a negative specimen and a repeat curettage finally confirmed the clinical impression of malignancy.

4. We have found aspiration curettage invaluable in diagnosing recurrent activity in the postradiation inoperable group of cases.

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463 North Oak Street

ENDOMETRIAL HYPERPLASIA PRODUCING A SYNDROME SIMULATING EARLY PREGNANCY

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DURING the course of a review of 1,092 cases of endometrial hyperplasia treated at the Sloane Hospital over a period of twenty-eight years (1921-1948), it was noted that a substantial number of these patients presented themselves to the clinician with such a symptom complex that a preliminary diagnosis of pregnancy, either normal or with one of its several complications, had been made. This special group comprised 75 patients, 6.9 per cent of the entire number of women with endometrial hyperplasia during this period.

A composite history of the patient with this syndrome is as follows: She is in the childbearing age, usually in the twenties or thirties, and has had previous and successful pregnancies. Her periods have been entirely regular and normal, when for no apparent reason her menses cease. Knowing that the possibility exists, the patient assumes that she is pregnant. After a latent period of one, or two, or even three months, she suddenly starts to have vaginal bleeding for which she seeks medical attention. On pelvic examination the cervix and uterus are found to be somewhat softened and the corpus is usually described as slightly enlarged. The natural diagnosis is threatened or incomplete abortion and a dilatation and curettage are performed. When the curettings are examined in the laboratory, however, the histologic diagnosis is hyperplasia of the endometrium.

An individual illustrative case history is as follows:

Case Report

Mrs. J. L., was a 28-year-old Negro woman, gravida iii, para iii, whose three deliveries had occurred at the Sloane Hospital, the last being two years before the present admission. The first delivery was uneventful; the second and third complicated by puerperal endometritis. The menstrual periods had begun at 13 years and occurred at twenty-eight-day intervals, lasting four days.

She sought attention on Nov. 18, 1938, with the history of amenorrhea of two months, followed by profuse vaginal bleeding for eight days. The menstrual period for August had been normal, that for September only a slight show, and none had occurred in October. The patient had suspected pregnancy and had taken large amounts of caster oil for induction. There was slight bleeding after the catharsis followed by profuse bleeding on Nov. 10, 1938.

On examination the cervix was irregular and soft and the uterus the size of a six weeks' pregnancy. Both adnexa were described as thickened. With a diagnosis of incomplete abortion, a dilatation and curettage were performed on the day of admission. Microscopic examination of the curettings revealed cystic glandular hyperplasia of the endometrium.

The patient was not seen again until 1940 when she presented herself in a gravid condition to the antepartum clinic. History at this time revealed that following the previous curettage her menses resumed their former regularity. This pregnancy ended in a term delivery in July, 1940. She became pregnant again in 1941 but miscarried at the twelfth week. A curettage revealed chorionic villi.

The patient was last seen in the gynecology clinic in July, 1942, at which time her periods were regular and of a normal amount, but occurring every twenty-one days.

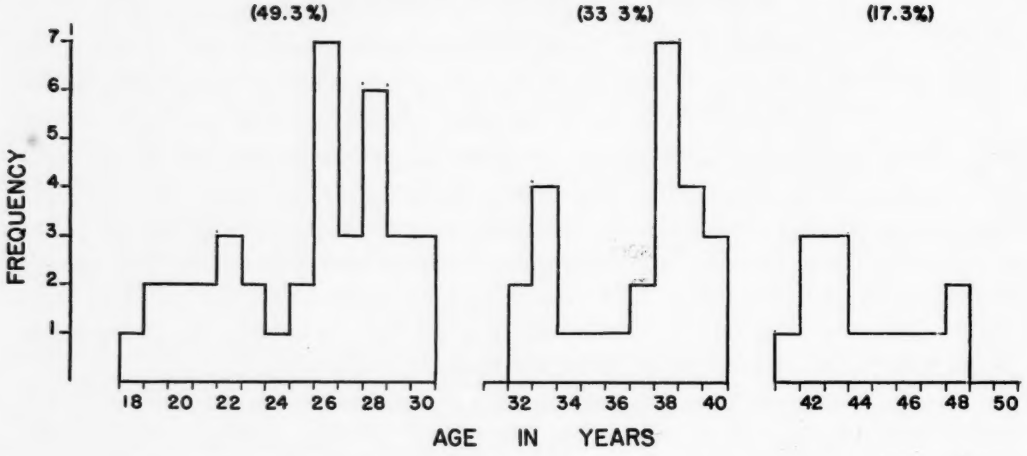

FIGURE 1. AGE DISTRIBUTION BY DECADE

Not all of these patients received the diagnosis of incomplete abortion. Three were suspected of having ectopic pregnancies and were operated upon with this diagnosis. In addition, four patients underwent dilatation and curettage for missed abortion, while six others for a variety of medical indications submitted to a curettage for the termination of the supposed pregnancy. Of the latter ten patients none had vaginal bleeding but simply an abrupt cessation of menses with suggestive physical findings.

TABLE I. PREOPERATIVE DIAGNOSIS

DIAGNOSIS	NUMBER
Incomplete abortion	62
Ectopic pregnancy	3
Missed abortion	4
Pregnancy—therapeutic abortion	6
Total	75

Fig. 1 shows the age distribution of these patients by decades. Thirty-seven, or 49.3 per cent, of these patients were 30 years of age or younger; twenty-five, or 33.3 per cent, were between 31 and 40 years of age; while 13, or 17.3 per cent, were over the age of 40 years.

The question of the fertility of such a group of patients as this is of considerable interest. Twenty of these women had never been pregnant. The other fifty-five had 152 pregnancies, of which ninety-seven, or 63.8 per cent, had been successful. The fifty-five pregnancies terminating in abortion gives an absolute abortion rate of 36.2 per cent. This may seem very high and particularly significant. But when one reviews the obstetrical histories as recorded, it is noted that fully half were illegally induced. Therefore, the relative rate excluding the inductions must be considerably lower and no doubt would more

Fig. 2. Fig. 3.

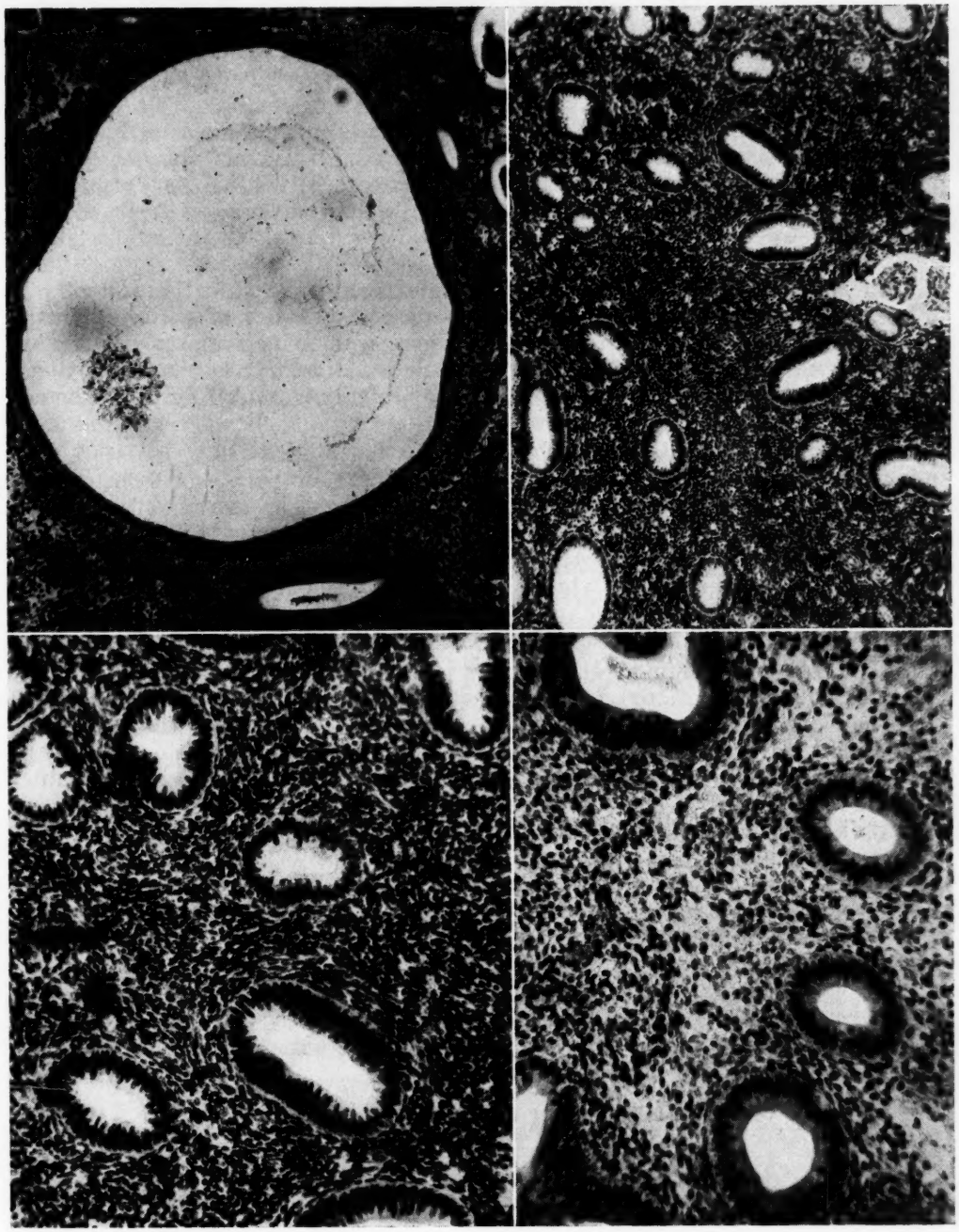

Fig. 4. Fig. 5.

Fig. 2.—Representative photomicrograph of microscopic findings on the curettings from the patient in the illustrative case history: cystic glandular hyperplasia (×50).

Fig. 3.—Same patient: Another area demonstrating glandular hyperplasia without dilatation (×50).

Fig. 4.—Same patient. A greater magnification of the glandular epithelium showing pseudostratification and nuclear elongation. In this area the stroma is dense and active (×150).

Fig. 5.—Same patient. Another area under higher magnification shows the presence of moderate stromal edema (×150).

truly reflect the inability of these particular patients to maintain a successful pregnancy. Moreover, there is the possibility that some of these previously recorded abortions were also due to hyperplasia and that conservative management without operation failed to establish the true diagnosis.

TABLE II. PREVIOUS PREGNANCIES IN 55 PATIENTS

	NUMBER	PER CENT
Successful	97	63.8
Unsuccessful	55	36.2
Total	152	100.0

The physical findings are of interest and help to explain the difficulty in differential diagnosis. By far the most common observation was slight enlargement and softening of the uterus, this occurring in forty patients. Softening of the cervix was described in thirteen, while in only three patients was Chadwick's sign noted as present. In only three patients were A-Z tests performed and these all were reported as negative.

The microscopic sections on all these patients have been reviewed. Although there has been a highly variable degree of hyperplasia from one patient to another, and at times from one area to another in the same patient, all demonstrate the characteristic changes to which we apply the name "glandular hyperplasia." The curettings from thirty-nine patients demonstrated cystic glandular hyperplasia while those from the remaining thirty-six showed hyperplasia of the adenomatous type. In no case was it necessary on re-examination to alter the original microscopic diagnosis.

The most surprising revelation was the appearance of a later pregnancy in certain of these patients. Subsequent to the appearance of this syndrome, thirteen women underwent sixteen pregnancies in the Sloane Hospital, thirteen of which were successful. Since this demonstrates that a later pregnancy is entirely possible in a woman who has had endometrial hyperplasia, and since it is not the universal custom for American women to remain rooted in one locale for their childbearing years or even invariably seek out the same institution for subsequent obstetrical care, then it is entirely possible, and probable, that these figures are lower than the true incidence of subsequent pregnancies in this group. Moreover, sufficient time has not elapsed for those younger women observed during recent years to have had ample opportunity of demonstrating their fertility.

TABLE III. KNOWN SUBSEQUENT PREGNANCIES IN 13 PATIENTS

	NUMBER
Successful	13
Unsuccessful	3
Total	16

Discussion

The description of this syndrome would be of far less significance were the majority of the patients at either end of the reproductive life. For it is at these periods in a woman's existence that we most commonly expect, and see, irregular periods of amenorrhea and menorrhagia resulting from hyperplasia of the endometrium.

The age distribution being as described, however, with the vast majority of the patients in the twenties or thirties, we must explain the mechanism of

the production of this syndrome without relating it to the early pubertal years or to the menopause even though its pathogenesis may be similar.

Accepting as valid the well-substantiated concept that endometrial hyperplasia results from the sustained and unopposed action of estrogen[1-4] and that this is seen physiologically in association with the anovulatory cycle,[5, 6] we must come to the conclusion that it is the appearance of the anovulatory cycle which is of prime importance.

The cause of the anovulatory cycle is as remote among these patients as it is among all patients with hyperplasia of the endometrium. Whether at this time the persistence of an unruptured follicle is the primary fault or rather an imbalance in the pituitary-ovarian relationship, we cannot say. Certainly nothing in this study can enlighten us in that respect.

Therefore, we must postulate that, in these women who have a known fertility of a reasonable degree and no menstrual irregularity, for some yet unknown reason anovulatory cycles appear with prolongation of the estrogen effect, amenorrhea, endometrial hyperplasia, and subsequent menorrhagia. The clinical manifestations of this process often lead the consulting gynecologist to make an erroneous diagnosis of early pregnancy, usually with one of its more common complications. We know that the anovulatory cycles need not persist, because of the later pregnancies.

Summary

1. A syndrome is described in which endometrial hyperplasia created such a symptom complex in women of the reproductive age that a diagnosis of pregnancy, either normal or with one of its several complications, was made.

2. The syndrome consisted of normal periods, amenorrhea of one to three months, and menorrhagia.

3. Physical findings usually consisted of uterine bleeding and a slightly enlarged and softened uterus.

4. Microscopic examination revealed hyperplasia of the endometrium.

5. Subsequent pregnancy occurred in thirteen patients.

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54 Noxon Street.

Department of Case Reports
New Instruments, Etc.

A NEW COLPOSTAT FOR THE RADIUM TREATMENT OF CARCINOMA OF THE CERVIX*

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A NEW applicator for the local radiation treatment of cancer of the cervix is described which, while maintaining the advantages of applicators heretofore used, makes possible the application of radium or radon with a high degree of accuracy without the use of extensive or complicated apparatus. The technique used with this applicator adheres strictly to the fundamental principles of the radiological treatment of cancer of the cervix as originally enunciated by Regaud.

The treatment of cancer of the cervix I believe is primarily a radiological problem. This fact was well established in the 1920's when Regaud made his great contribution to this branch of therapy; and even though in the last few years operative procedures are being revived and extended because of the great advances in surgery and the many more facilities now available to the surgeon, the primary advantages of proper radiation therapy have not been lessened.

The delivery of the cancer lethal dose to the cervix proper presents no problem since the cervix is so easily accessible; but the radiation of the parametrial triangle is a very definite problem that must be met by bringing the centers of activity in close proximity to these structures. Regaud and his co-workers designed applicators to radiate the cervix and parametrium from the uterine cavity and from centers of activity placed in the lateral fornices and against the external os.

The original Regaud applicators consisted of one uterine tube activated from the fundus down to the external os and three corks. Each cork was provided with a cylindrical cavity to accommodate a radium or radon capsule. One cork was placed in each lateral fornix and the third cork against the external os. The filtration was 1.0 mm. platinum in the uterine canal and 2.0 mm. platinum in the corks. The treatment was given over a period of seven days of continuous application and a minimum dosage of 6,000 millicurie hours was given. The results of this method of treatment actually established radiation as the method of choice in the treatment of carcinoma of the cervix.

The modifications that have been made in these applicators in all these years are well familiar to the radium therapist and need not be enumerated here. These modifications included spring colpostats, metal expanding colpostats, hard rubber ovoids, etc. The advantages and disadvantages of each are well known.

During the last ten years we have had in this country both a pessary and Y-colpostat made of Ametal rubber and holding two ovoids for the lateral fornices. The third ovoid and the uterine tube have been incorporated in one applicator of Ametal rubber in the form of an inverted-T. The tube is placed in the uterine canal and the ovoid abuts against the external os. This system has permitted good immobilization by packing.

*This applicator was developed and made to the specifications of the author by The Radium Emanation Corporation of New York.

In the new applicator that is illustrated in Fig. 1, the author has taken the Ametal rubber inverted T, mentioned above, and added to it, at the level of the center of the cross ovoid, two Ametal rubber arms at the end of which an ovoid is attached. In this manner all the centers of activity are contained in a single applicator consisting of uterine tube and three ovoids, each constituting an integral part of the applicator. The Ametal rubber arms joining the lateral ovoids to the cross ovoid are of sufficient thickness to provide the necessary rigidity to prevent positional changes, while they are thin enough to permit bending back at the time of insertion in the vagina. It must be noted here that Ametal rubber is not hard, but soft and pliable, yet provides rigidity with thickness. The technique of application is very simple. Fig. 2 shows, in section, a malignant cervix. A conservative conization of the cervix is done as shown in Fig. 3, and the applicator is introduced and placed in the position shown in Fig. 4. It is not necessary to carry out the conization of the cervix; but the author prefers it for two reasons: first, because the cross-ovoid can be placed actually in the cervix; and second, because, grossly, quite often the extent of invasion may be ascertained.

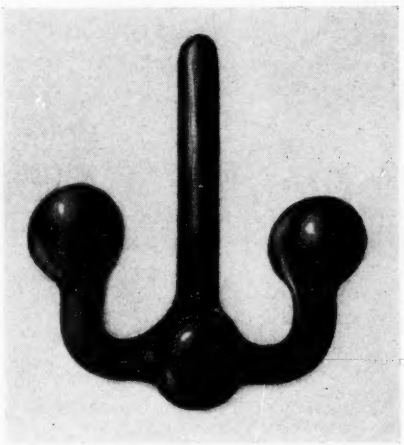

Fig. 1.

When pressure is applied by packing, the lateral ovoids are pushed laterally and upward, thus bringing them more closely to the parametrial area that is so important in this method of treatment. The proper position of the applicator is shown in Fig. 4 and the applicator in section is shown in Fig. 5, indicating the manner in which the radium or radon capsules are distributed.

The proper position of the applicator is maintained throughout the treatment period by packing, and the applicator remains in its proper position because its design does not permit rotational motion or lateral displacement. The applicator, therefore, overcomes the objection of possibility of positional change of the radium or radon tubes, both actual and in relation to one another.

With this arrangement, we can then proceed to vary the actual radium or radon distribution in the tube and ovoids depending upon the requirements of each case. The most commonly used distribution, when the anatomy is as shown in Fig. 2, is as follows: three tubes of 10 mg. each in the uterine tube; one tube of 5 mg. in the cross-ovoid; and one tube of 10 mg. in each lateral ovoid. This distribution is in accordance with the original Regaud method.

I employ dosages of 8,000 to 10,000 millicurie hours over periods of from 6 to 10 days. This means continuous application with no interruption. In some

institutions the Regaud technique is modified to the extent of delivering the total dosage in two sessions one week apart. However, I prefer to adhere strictly to the Regaud dictum of high dosage in one continuous treatment and I have found no objection to this method when the physical factors of the applicator, as described here, are rigidly maintained.

To forestall temperature rise due to poor drainage, the applicators had to be removed, resterilized, and immediately reinserted every 48 hours during the treatment. However, since the advent of the antibiotics one does not have to undertake this procedure more than once in an application lasting 8 to 10 days.

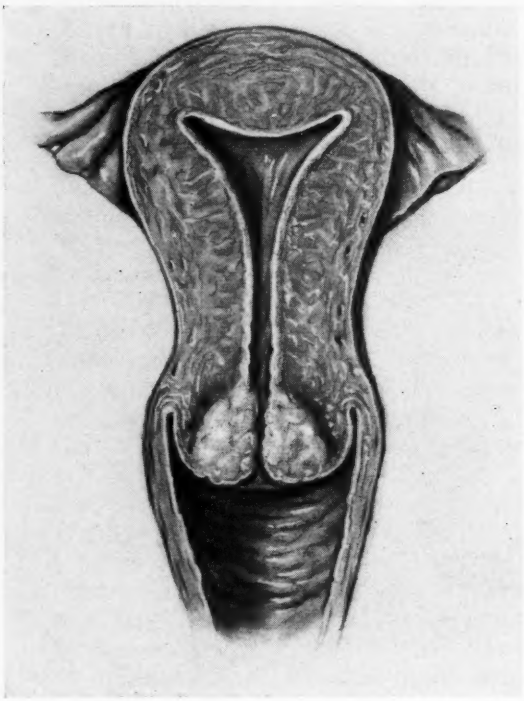

Fig. 2.

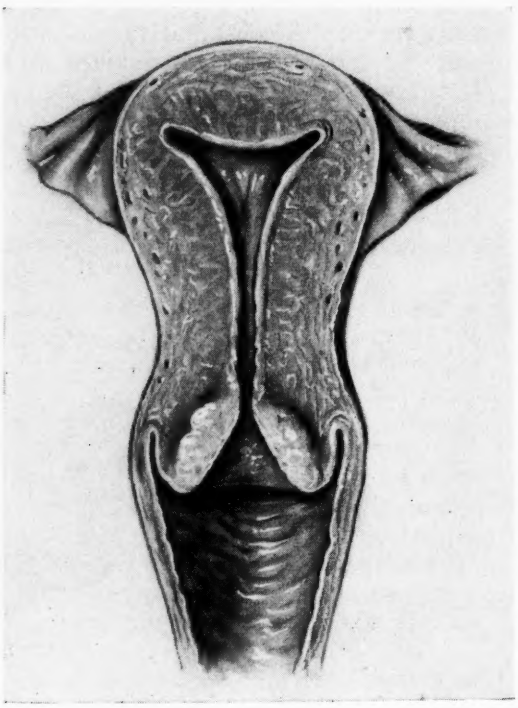

Fig. 3.

The applicator here described may be made in any size, but I have found, by measurement both in patients and in cadavers, that the most satisfactory is the one here illustrated. It has a tube length of 5 cm. and an over-all length of 5.5 cm., the diameter of the cross-ovoids is 1.7 cm., and the actual length of each of the three ovoids is 3.0 cm. The active length of the tube in each ovoid is 1.8 cm. A very important dimension is the distance between lateral ovoids. In the applicator here illustrated this distance is 5.0 cm. This distance may become 5.5 cm. when the packing pressure separates the ovoids slightly.

With the dosage and distribution described, the amount of radiation at the vaginal wall remains within limits of tolerance. Considering the cancer lethal dose as the accepted figure of 6,000 gamma roentgens, the dose at the cervix is of the order of three to four times the cancer lethal dose; and at the region of the obturator nodes of the order of one-third to one-half the cancer lethal dose. While the dose at the cervix is apparently very high, no damage is done because the cervical tissues can absorb extremely high dosages. It is believed that this high dosage is very much in order because of the tendency of carcinoma of the cervix to recur when dosages are limited to amounts of the order of the cancer lethal dose.

I wish to call attention to the absence of so-called intense radiation reactions following the technique here described. Bladder and rectum are practically automatically protected when the applicator is inserted properly because distances to rectal and bladder mucosas from active tubes are safe and maintained so during the entire treatment period. Moderate cystitis and proctitis are natural sequelae to this treatment; but the severe proctitis, cystitis, vaginitis, followed by breaking down of tissue, do not constitute reactions that one must expect if the treatment is properly carried out. Another feature that contributes to the value of this applicator is its light weight so that the pressure from its weight is practically negligible in comparison to the pressure exerted by packing gauze. The applicator is easily handled and can be inserted accurately by anyone versed in gynecological procedure.

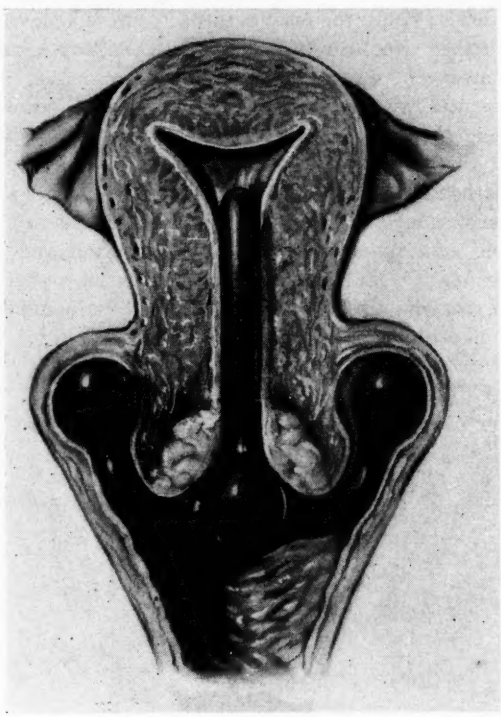

Fig. 4.

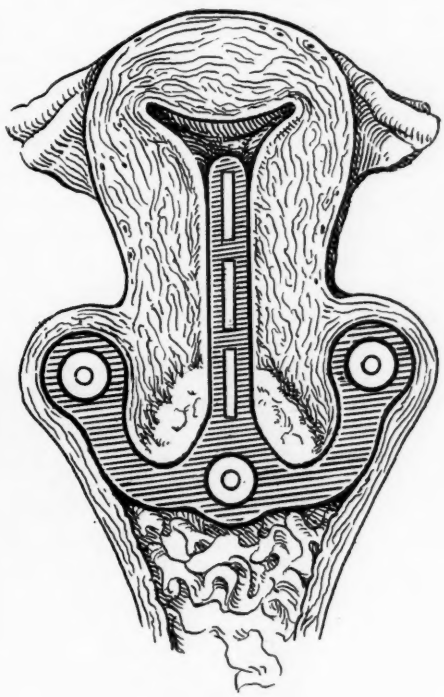

Fig. 5.

Summary

An Ametal rubber applicator is presented for the treatment of carcinoma of the cervix in accordance with the Regaud technique, which incorporates these advantages: (1) all the centers of activity, intrauterine and vaginal, are carried in a single applicator; (2) absence of shift in actual and relative position of radium or radon tubes during the period of treatment; (3) simplicity of application and immobilization.

1103 Park Avenue.

FIBROSARCOMA IN THE SITE OF BARTHOLIN'S GLAND

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OF THE malignancies of the female genital tract, those of Bartholin's gland and the surrounding region escape with the distinction of being the least recorded or observed.

A 31-year-old, well-developed, well-nourished Negro woman entered the Cook County Gynecological Clinic on Jan. 18, 1950, complaining of an extremely tender mass in the right labia majora. She was admitted to the hospital with a diagnosis of Bartholin's abscess. Patient gave a history of a small palpable nodule in the right labia for two years. This caused her no trouble until the present time.

Two months previous to admission to the hospital, the patient recognized mild pain on walking and noted that the area had become larger, increasing from bean size to that of a walnut. These symptoms increased one month before entry to the hospital, and she noted the mass growing larger and more painful on walking or standing for long periods of time. One week before entry, the mass was the size of a lemon and the pain unbearable. The patient complained of painful hemorrhoids and frequency of urination.

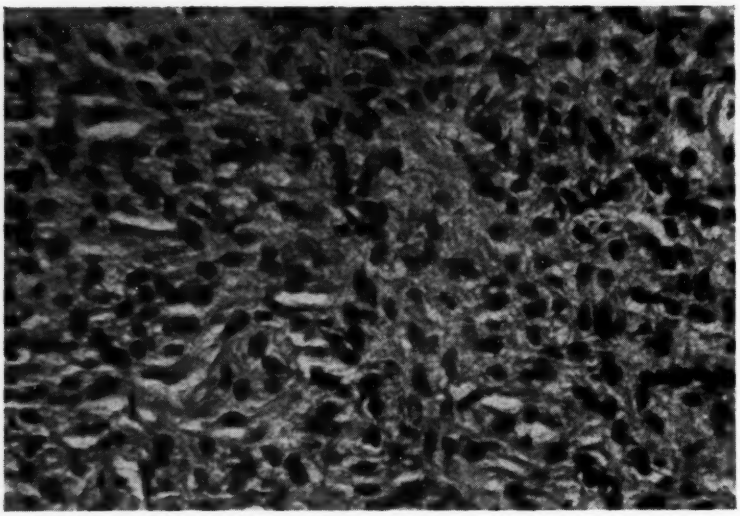

Fig. 1.

Findings consisted of slightly palpable superficial supraclavicular lymph nodes, bilateral enlarged, tender inguinal lymph nodes, and tenderness and positive Murphy punch over the right kidney and flank.

A large, tender fluctuant mass was located in the area of Bartholin's gland on the right side. The mass occluded the vaginal orifice.

Rectal and vaginal examinations were deferred because of extreme pain and tenderness. Urinalysis was negative. The patient had positive Kahn and Wassermann reactions.

Immediate incision and drainage were done. Three hundred thousand units of penicillin in oil and hot sitz baths were given, and local moist heat was applied.

She was released from the hospital the following day and sent to the gynecological clinic. She received an additional 300,000 units of penicillin the day of release from the hospital.

Inspection revealed a fungating, infected mass in the site of Bartholin's gland which measured approximately 6 by 5 by 5 cm. Punch biopsy was taken; the patient was put on penicillin and instructed in the use of warm moist applications. The report of the biopsy indicated a spindle-cell fibrosarcoma. Papanicolaou smears taken on first admission were negative. The patient returned the following week, and the lesion looked smaller and somewhat improved.

The patient was readmitted to County Hospital, and a vulvectomy was done. Serial sections following vulvectomy revealed spindle-cell fibrosarcoma in the site of Bartholin's gland. It is quite probable that the neoplasm replaced Bartholin's gland, as no Bartholin's gland tissue could be found on section.

58 East Washington Street

A MALIGNANT GRANULOSA-CELL TUMOR ASSOCIATED WITH PREGNANCY

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LEXINGTON, KY.

(From the St. Joseph Hospital)

FROM the literature it appears that there have been approximately 350 cases of these tumors reported to date. They represent somewhere between 2.5 and 4 per cent of all ovarian neoplasms. Ninety per cent of these are unilateral. Estimates as to malignant changes vary from 10 to as high as 55 per cent.

Jones and Te Linde, in reviewing the curability of granulosa-cell tumors, brought to our attention, and strikingly so, how many years afterward this type of tumor may recur. They cited three cases occurring fifteen, sixteen, and nineteen years, respectively, after the original operation.

We believe that our case represents the only one ever reported of a very highly malignant granulosa-cell tumor, associated with pregnancy, which resulted in the death of the patient in only a few weeks after it had been diagnosed. This tumor was diagnosed prior to operation without the assistance of hormonal studies. The facilities for obtaining these were not available.

Mrs. A. W., 27 years old, white, was admitted to a Lexington hospital on Oct. 4, 1949, complaining of enlarged painful breasts and upper back pain of one month's duration. Her last menstrual period had occurred June 11, 1949, approximately four months prior to her admission. Except for a moderate amount of nausea and vomiting, her condition was unremarkable till one month prior to her admission when she began having a constant aching pain in the right interscapular area. Within a few days following the onset of this pain, she became aware of two small tender nodules in the upper outer part of the left breast. These nodules gradually became larger, more painful, and more numerous. At the same time nodules would appear and disappear in the right breast which was also becoming tender and enlarged. As the breasts enlarged, the back pain persisted to such an extent that it confined her to bed. In spite of prescribed medications her complaints became more severe and she was finally referred to the care of the senior author. There had been no history of fever nor any complaints relative to the gastrointestinal, urological, or neurological systems.

In the past the patient's general health had been unremarkable. She had had an appendectomy and a tonsillectomy at the ages of 7 and 11 years. She had had a normal pregnancy in 1941 and a spontaneous abortion when three months pregnant in 1948. Menstrual periods had begun at 13 years and had been regular, occurring every twenty-six to twenty-eight days, lasting five days, with only slight associated discomfort.

On admission the patient appeared moderately ill with a temperature of 98.8° F., pulse 94, respirations 20, and a blood pressure of 120/50. The head and neck were essentially normal except for a few dental caries. Lungs were clear and heart normal. Both breasts were markedly enlarged, the left more so than the right. The breast tissue was firm, nodular, and tense with extreme tenderness to palpation. The nipples were erect and slightly enlarged. The areolae were darkened and enlarged. In both axillae were small palpable nontender lymph nodes. The abdomen was slightly enlarged with the fundus of the uterus palpable almost to the umbilicus. In the left lower quadrant was a small mass separate from the uterus and slightly tender to deep palpation and presumed to be fecal. There was slight tenderness over the vertebral bodies T-7 to T-10. Pelvic examination revealed an enlarged uterus consistent with a four months' pregnancy. Reflexes were normal throughout.

On admission, analysis of a catheterized urine specimen revealed straw-colored normal urine. The red blood count was 3.8 million; the hemoglobin 10.5 Gm.; the white blood count 15,150 with 9 per cent stab forms, 55 per cent segmented neutrophiles, and 36 per cent lymphocytes. A chest x-ray revealed slight pleural thickening and minimal hypertrophic arthritis in the dorsal spine.

Repeated enemas failed to change the palpable mass in the left lower quadrant of the abdomen. On the fourth day of hospitalization the patient was unable to void and required catheterization. When she attempted to sit on the edge of the bed, it was noted that she had developed marked weakness of both lower extremities with paresthesia of the left leg.

It was considered that the patient had a granulosa-cell tumor of the left ovary, and a pelvic laparotomy was indicated.

On Oct. 9, 1949, the abdomen was explored through a small midline incision. The uterus was found slightly to the right of the midline and was of the size and consistency of a four months' pregnancy. In the left adnexal region there was a solid tumor mass measuring 10 by 8 by 7 cm. incorporating the ovary. Lying in the tubo-ovarian ligament inferiorly was a hard nodule the size of an almond. In the right adnexal region there was found a similar-appearing tumor mass measuring 8 cm. in diameter with what grossly appeared to be a small amount of normal ovarian tissue visible. The left adnexal tumor was excised and the abdomen closed.

The patient withstood the operative procedure well and had an uneventful postoperative course. Following the operation she appeared slightly improved. However, the lower extremities became progressively weaker until by Oct. 14, 1949, she had complete flaccid paralysis with loss of sensation below the middorsal area. A spinal puncture at this time revealed an initial pressure of 160 mm. of water with a negative Queckenstedt test. The spinal fluid was found to be clear with a cell count of five white cells (100 per cent lymphocytes) and a total protein of 240 mg. per cent. For palliative therapy, x-ray radiation was begun on the breasts and dorsal area of the back. This resulted in slight improvement in the tenseness of the breasts and slight relief of the constant back pain. The patient, however, became progressively weaker and finally expired in coma on Oct. 27, 1949.

Pathology

Gross.—The tumor from the left ovary measured 10 by 8 by 7 cm. Small nodules were also included from the left tubo-ovarian ligament. The large tumor completely replaced the ovary. The surface was slightly lobulated, and at one place the capsule was discolored. On section, the tumor was cut with little resistance and the surface of the cut section was white and translucent. There was an infarct beneath the capsule in one area, measuring 3 by 3 by 2.5 cm.

Histopathology.—Sections from the large tumor showed it to be quite cellular. The cells were large, had large moderately hyperchromatic nuclei, and mitotic figures were fairly frequent. An occasional poorly formed rosette could be recognized. The infarcted area showed complete necrosis of the tumor cells. There was little stroma and a fairly abundant blood supply. Sections from the tubo-ovarian ligament showed this tumor to have the same structure as the ovarian mass.

Diagnosis.—Malignant granulosa-cell tumor with local metastasis.

An autopsy was performed on the unembalmed body approximately two hours after death. The important findings at autopsy were as follows:

Gross.—The body showed a marked degree of emaciation, with little subcutaneous fat. The breasts were extremely firm and nodular.

Internal.—The spleen was approximately five times normal size, firm and dark red. The mesenteric, pelvic, and aortic nodes were enlarged and white. The right ovary contained a firm, white tumor mass measuring 8 cm. in diameter. The ovarian tissue appeared entirely replaced by the tumor. A mass of firm white tissue was found in the interspace between the sixth and seventh ribs at the costovertebral articulations on the right. This tissue appeared to infiltrate between the articulations into the spinal canal and to compress the cord. The

breast tissue was exceedingly firm and white. The uterus reached to the umbilicus and contained a normal fetus, 16 cm. in length.

Microscopic.—The microscopic examination showed the breast, liver, spleen, pancreas, kidneys, and leptomeninges of the mid-thoracic cord to be infiltrated with small dark cells. These masses of cells resembled the cells of the tumor of the left ovary which was surgically removed. These same cells replaced the normal tissue of the right ovary and were found in the pelvic and aortic lymph nodes. Most remarkable was the diffuse infiltration of the breast tissue by these atypical cells. It was this infiltrate which caused the extreme firmness and nodularity of the breasts. The tumor cells were seen growing in masses without any evidence of structural formation. In some areas, small cystic spaces, characteristic of the Call-Exner bodies, were found.

Autopsy Diagnosis: 1. Malignant granulosa-cell tumor of the left ovary with metastasis to left broad ligament, mesenteric and aortic nodes, right ovary, kidney, spleen, pancreas, liver, thoracic cage, leptomeninges of spinal cord, and breasts. 2. Infarct of spinal cord at level of metastasis. 3. Gravid uterus, four months' pregnancy.

Reference

Jones, G. E. Seegar, and Te Linde, Richard: Am. J. Obst. & Gynec. 50: 691, 1945.

PRIMARY ADENOCARCINOMA, PAPILLARY, OF FALLOPIAN TUBE

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THIS case is being reported because it represents a relatively rare lesion, particularly in the age group of this patient.

The patient, a 74-year-old white woman, was seen first in January, 1950. Her chief complaints were as follows: (1) pain in right lower quadrant for the past three months, getting gradually worse, most noticeable when she sat down, rose, or bent forward, and relieved when she assumed a recumbent position; (2) a sense of weight in lower abdomen when in an upright position; (3) a palpable mass in the right lower quadrant which caused sharp pain when she touched it with her hand, or attempted to move it; (4) frequency and burning on urination; (5) a six-pound weight loss in the previous few months; and (6) no vaginal discharge or bleeding.

Physical Examination.—On inspection the right lower quadrant was higher than the left. A palpable mass was easily discernible in the right lower quadrant, which was rather tender to palpation. On bimanual examination, this mass was smooth, movable, and to the right of the uterus.

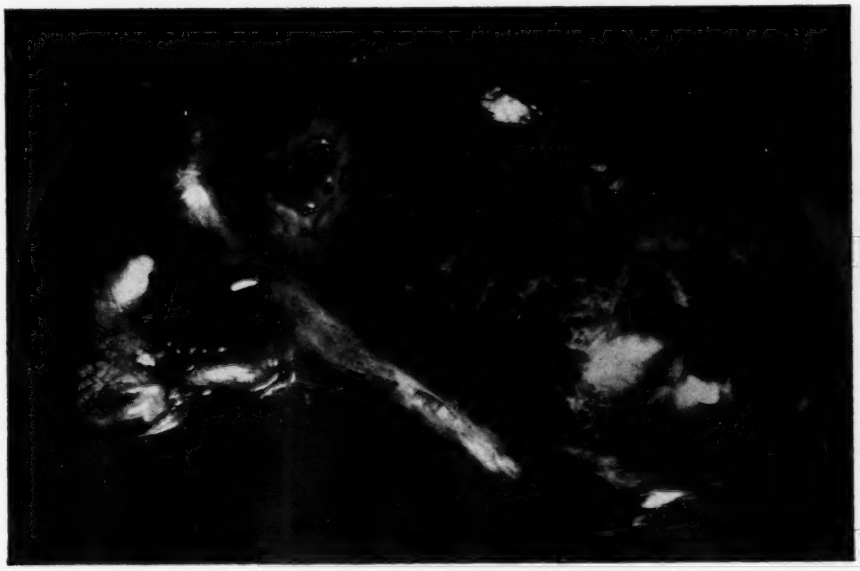

Fig. 1.—Gross specimen and site of pedicle.

Past History.—The patient was married, but had no children. She had vaginal bleeding at 23 years of age. She ceased menstruating at 38 years of age. The remainder of the examination was of no special significance. There was a mild anemia.

On Jan. 18, 1950, she was operated upon by the senior author (A. N.) at Mount Sinai Hospital under spinal anesthesia. After the abdomen was opened, a huge, cystic, movable mass appeared which was greenish red. It was attached to the lateral abdominal wall in the right lower quadrant. No fluid, adhesions, metastases, or other obvious abnormalities were

seen or felt. The base of the pedicle was clamped doubly and the mass removed. It resembled a huge hydrosalpinx. The pedicle was transfixed, ligated, and then peritonized and the abdomen was closed in layers.

The patient made an uneventful recovery and was discharged on the twelfth postoperative day, Jan. 30, 1950.

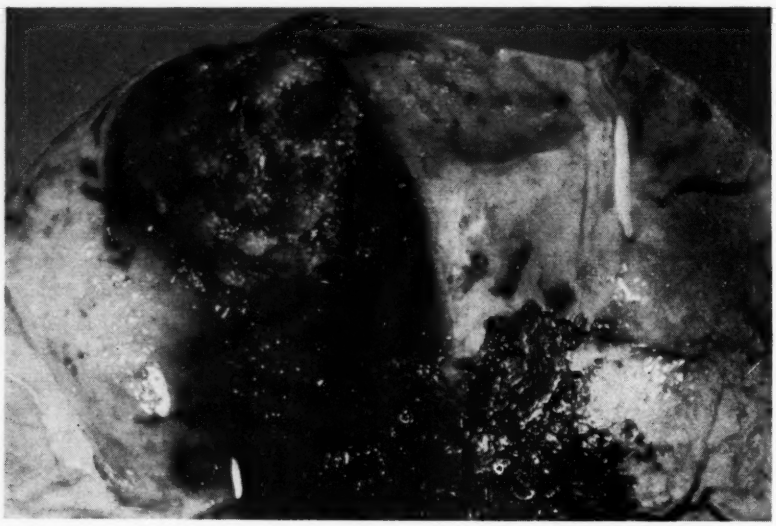

Fig. 2.—Gross lesion as it appeared when tube was opened.

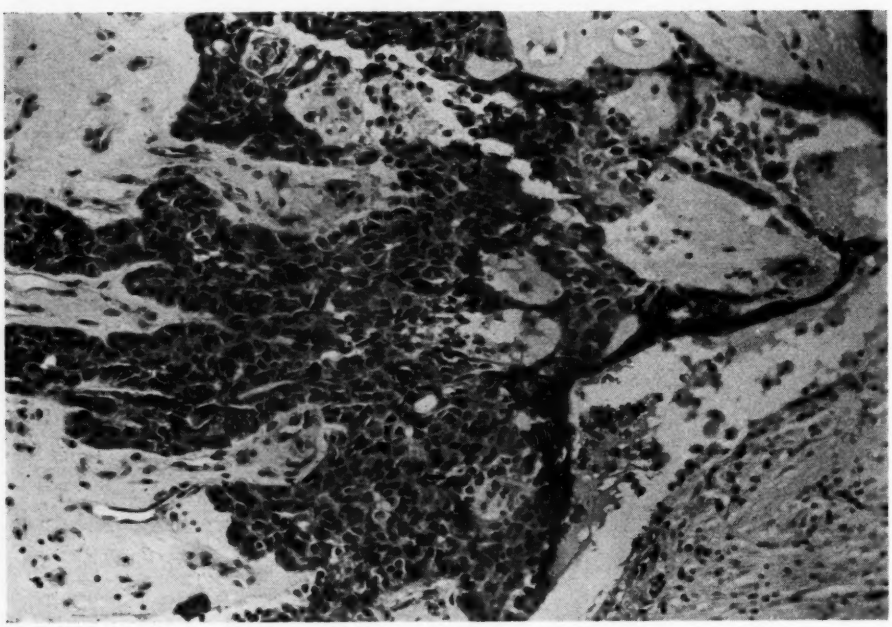

Fig. 3.—Microscopic section of tumor.

The true nature of the lesion was not suspected until the specimen was examined in the department of pathology.

Pathological Examination.—The specimen was a retort-shaped Fallopian tube which measured approximately 20 cm. in length and 9 cm. in diameter at the widest portion. The

abdominal ostium was completely closed. The serosa was smooth and injected. When the tube was opened, a large amount of green semisolid material was noted in the lumen. At the proximal end of the tube and occluding its lumen, there was a cauliflower-shaped, friable tumor mass measuring 2.5 by 2 cm. in dimensions. Elsewhere the inner lining of the tube was covered with hemorrhagic and necrotic material. Small remnants of ovarian parenchyma were noted at the distal end of the tube.

Microscopic examination showed the tumor mass to be contained within the lumen of the tube. It was a cystic papilliform growth. The lining cells had dense hyperchromatic nuclei. The nuclei varied in size, shape, and staining reaction. There were moderate numbers of mitoses. The cells were supported on an edematous, moderately dense, fibrous-tissue structure. In the area of the tumor in the lumen of the tube were desquamated tumor cells, red blood cells, and acute inflammatory cells. The tubal wall, where uninvolved, was thin, densely fibrous, and infiltrated with lymphocytes and a few polymorphonuclear leucocytes. There were also many mononuclear cells present which contained brown pigment granules in areas near the tumor. The tumor did not penetrate the wall. The ovary showed several psammoma bodies, hyalinized follicles, and arteriosclerotic blood vessels in a dense fibrous-tissue stroma. The lesion was classified as a papillary adenocarcinoma of the Fallopian tube.

Summary.—A primary papillary adenocarcinoma of the Fallopian tube was found in a 74-year-old nulliparous woman. There was no evidence of metastases or spread at the time of operation. The clinical manifestations were similar to those of an ovarian cyst.

Recent literature has been covered by: Hu, C. Y., Taymor, M. L., and Hertig, A. T.: Am. J. Obst. & Gynec. **59**: 58, 1950.

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AN INFLATABLE TIP AND OTHER MODIFIED INTERCHANGEABLE TIPS FOR THE TRIGGER CANNULA USED IN THE STUDY OF FEMALE STERILITY

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THE modified self-retaining trigger cannula with interchangeable tips provides the operator with a selection to further increase "versatility to meet every contingency" in tubal insufflation and uterosalpingography.[7] In addition, tips are provided for hysterometry and endometrial biopsy for which the cannula handle is well suited.* (Fig. 1.)

The flexible tips, modified from Hyams and Neustaedter, are narrower than the malleable tip and require no previous bending or rotation to conform to variations in flexion or version of the uterine body.[2, 3] Nor does the cannula have to be held at a particular angle to introduce them successfully. Instead, these tips conform to the contour of the cervicouterine canal automatically. The rubber acorn obturators are set directly behind the tip connectors and the collars are tightened to prevent slipping as the cannula engages the traction tenaculum. This also limits the length of rigid shaft within the cervical canal. Depth of penetration is determined first and the proper extension tip is selected. Bimanual examination and the hysterometer tip to sound the depth of the canal precede any attempt at cannulization.

Though very flexible, the tips do not buckle, compress, or become dislodged. This statement is based on very careful clinical testing. Those characteristics increase their usefulness in the presence of cervical stenosis or tumor within the uterine canal. In tubal plastic surgery where insufflation from below is desired, flexible tips do not hamper mobility of the uterine body, nor do they cause trauma. For this work, the plastic tips may be cut in special lengths. The flexible extension tips are interchangeable and are used exclusively with the inflatable obturator and new giant acorn. An acorn of this size could not be used with malleable tips because of the angle required for introduction. With flexible tips it is introduced with little difficulty and is readily cleared by the traction tenaculum. It is indicated in the troublesome giant gaping, lacerated cervix. It is a rubber acorn alternate for the inflatable obturator, especially where x-ray studies of the endocervix are required.

For those who prefer the original malleable tip for routine use, a set of tips may be made up bent at various angles between 120 and 160 degrees, which seems to be the range of variation of the cervicouterine angle in anteflexion and retroflexion. The acorn is not included in the bend. The stop collar (Jarcho[1]) is usually set 6.5 cm. behind the tip opening. However, this too is subject to previous examination.

The cannula is then held at the appropriate angle to introduce the tip into the cervix, from above in anteflexion and below in retroflexion. The cervix is steadied by the tenaculum. The angle that the cannula is held in relation to the cervix is termed the angle of introduction. This applies to any cannula employing malleable tips. This is emphasized here because it also applies to the

*The trigger cannula and the traction tenaculum are manufactured by the Clay-Adams Co., Inc., 141 East 25th St., New York, N. Y.

introduction of the hysterometer and biopsy tips which are similar. The trigger cannula also provides means for rotating the bent tips to conform to variations in version as well as flexion.[7]

The hysterometer tip is very pliable, with a rounded end to prevent perforation and to offer slight resistance at the internal os to measure the length of the cervical canal. This is done by advancing the sliding marker to the external os with a probe or applicator stick in a groove provided. The tip is withdrawn and the measurement taken. The tip is marked in centimeters. The tip is then reintroduced to the end of the uterine canal. From the two measurements the uterine index is determined.[4]

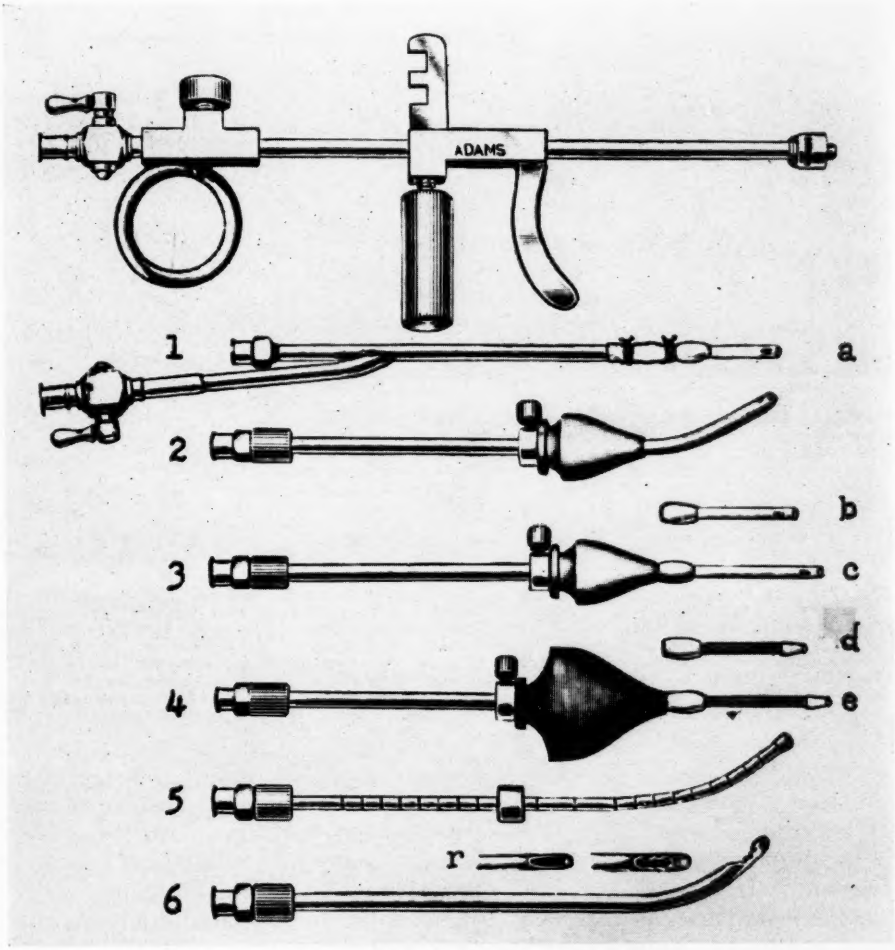

Fig. 1.—Trigger cannula with interchangeable tips: *1*, Inflatable tip. *2*, Malleable tip. *3*, Flexible plastic extension tips (Hyams): *a,b,c*, *4*, Flexible stainless steel extension tips (Neustaedter) *d*, *e*. Included in *4* is the new giant rubber acorn. *5*, Hysterometer tip. *6*, Novak and Randall (*r*) biopsy tips.

The multiserrated Novak and single-toothed Randall endometrial suction biopsy tips have been modified. They are now malleable so that they may be bent to conform to the cervicouterine angle and now are of the same width as the malleable tip. Combined with the fact that it may be rotated without changing the position of the thumb ring or trigger from the vertical, the tip is readily passed to any point in the uterine canal. Suction is applied as specimens of

endometrium are obtained with a curetting motion. The specimen is aspirated into the tip, which is then disconnected and placed in formalin, or the tissue is forced out first by syringe pressure or pressure from the suction machine.[5]

The inflatable tip devised for the trigger cannula (Fig. 2) is an adaptation of the Rubin-Myller inflatable cannula presented in 1948.[6] An important difference is that it inflates and deflates independently through a stem *(Q4)* controlled by a simple valve *(M1)*. The tip is, therefore, detachable as a separate cannula, as shown in insert, to be used in certain intact, nulliparous cervices after introduction and inflation are completed. In cases of hypoplasia, this is advantageous by reducing the length and weight of the cannula to a minimum. It is believed, in this form, to be the smallest self-retaining cannula available, since the intact external os maintains the inflated tip in place without the tenaculum.

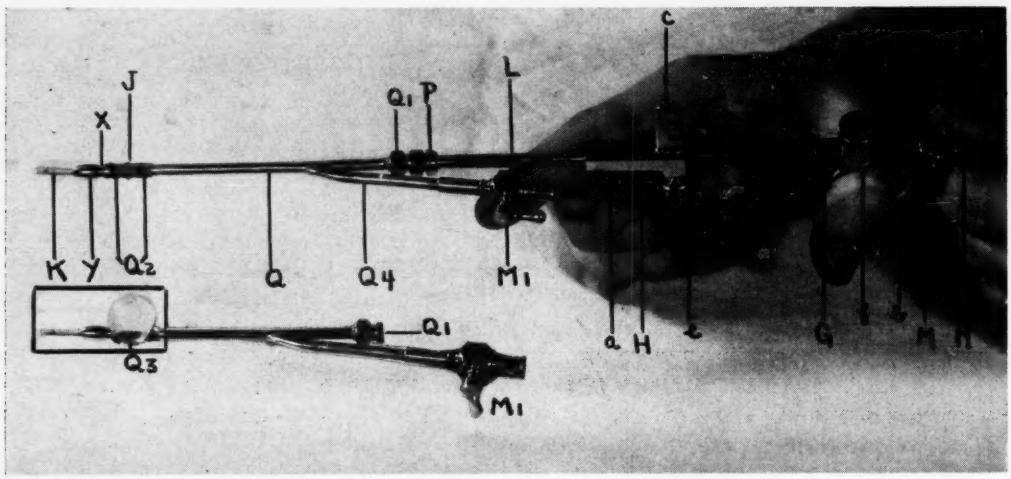

Fig. 2.—The inflatable tip attached to the trigger cannula handle. Insert shows the tip as an individual cannula. The balloon is inflated. Stem (*Q4*) and shaft (*Q*) conduct the water in and out of the balloon (*J*) through perforations (*Q3*) between the two grooves (*Q2*), controlled by valve (*M1*). An inner shaft, not visible, runs through shaft (*Q*) with no connection to the balloon. It conducts CO_2 or contrast medium directly to extension tip (*K*) which is attached at (*X*) by threaded connector (*Y*). When used as an individual cannula, a valve adapter similar to valve (*M*) is attached to hub (*Q1*) for fractional technique in uterosalpingography. For tubal insufflation, the rubber hosing attaches directly.

Another difference is that the independent system of inflation and deflation permits alterations in the volume of the balloon without interrupting the passage of CO_2 or contrast medium. It has been found that the majority of cervices require moderate traction by a tenaculum to hold the inflated balloon in place and prevent it from bulging out of the external os. This is thought to be due to the resilience of the cervical tissue and a tendency to dilate under the influence of balloon pressure.

The third difference is that the trigger cannula and traction tenaculum provide a means to apply self-retaining traction on the cervix. The technique, as shown below, is similar to that used with acorn obturators. Traction is always required when the cervix is lacerated and gaping.

Other differences are the use of flexible tips and the short length of the balloon which, like acorn obturators, is placed directly behind the extension tip to limit the length of rigid shaft in the cervical canal. This makes inflation more effective in short cervices and lessens the chance for trauma.

To determine the length of extension tip needed, measurement is made from the internal os. The shortest length, one inch (2.5 cm.), is the average. In very small uteri, connector *(Y)* alone may be used, first removing the Hyams tip.

The rubber tubing for the balloon fits rather snugly over the shaft *(Q)* when not inflated. This shaft is identical in thickness to the malleable tip. Introduction into the majority of cervices without previous dilatation is, therefore, the rule.

Inflation to "seal level" causes little discomfort to the average patient. More sensitive patients report moderate discomfort similar to a menstrual cramp. This soon subsides.

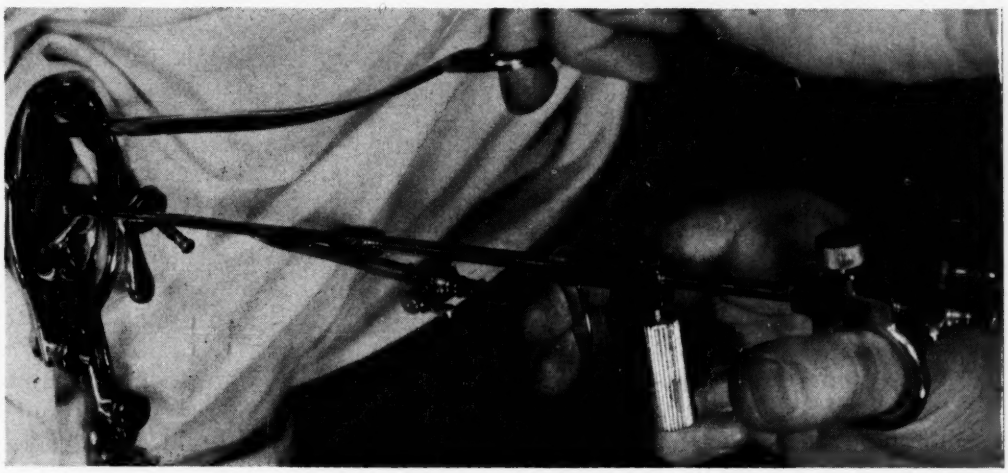

Fig. 3.—Introducing the inflatable tip. With the cervix steadied by the traction tenaculum, the tip is slid straight into the cervical canal until the balloon is slightly beyond the external os. The tenaculum is lowered momentarily on the cannula. The long set screw (Fig. 2, *e*) is loosened as the index finger is placed between it and the trigger (Fig. 2, *a*) in space (Fig. 2, *H*) to maneuver the notched wing (Fig. 2, *c*) under the tenaculum, engaging it in the upper notch. With the cross-bar (ratch) of the tenaculum so engaged, the index finger is again placed about the trigger and with gentle trigger squeeze, with the thumb through the thumb ring (Fig. 2, *b*), the tenaculum is made taut. The long set screw is then retightened.[7]

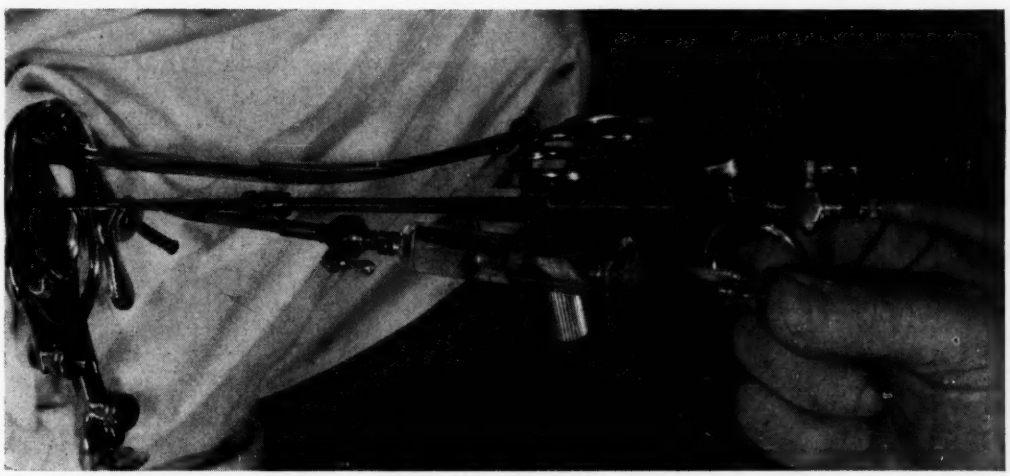

Fig. 4.—Inflating the balloon. A sterile 5 c.c. Luer Lok syringe filled with sterile water is attached to the stem. With the index finger hooked through the thumb ring for counter pull, the thumb pushes steadily on the syringe piston to inflate the balloon. The lower end of the balloon bulges slightly at the external os as inflation is completed. The volume of water needed varies between 1 and 4 c.c. Before releasing thumb pressure on the syringe, valve handle (Fig. 2, M1) is turned down to closed position. The syringe is then disconnected. To deflate, the syringe is reattached and the valve opened. The water flows back automatically.

To obturate a gaping cervix: The inflated balloon is pushed toward the internal os by gentle trigger squeeze. The thumb ring is first advanced to a point slightly behind the wing to provide a safety stop as with acorn obturators, described elsewhere.[7]

The use of the balloon is perfectly safe. Should it break, no harm can result, since it is filled with sterile water which drains into the vagina. It has been carefully tested and found capable of withstanding much more pressure and expansion than ever required. It will not fragment.

The need for replacing the balloon is a matter of judgment. With repeated boiling for sterilization, it has been used as many as thirty times without leakage. This was for the purpose of testing. As a practical rule, it should be replaced after ten tests. Replacement is quick, simple, and inexpensive. The special rubber tubing provided is cut slightly longer than the distance between the two grooves *(Q2)*. The extension tip is unscrewed, the tip area is lubricated lightly with soapy water, and the tubing is slipped over the end of the shaft at *X*. The balloon is then securely tied into the grooves by winding on surgeons' silk. A slight amount of slack is first allowed. The slack is noted as a slight elevation in the balloon *(J)*. This increases the molding quality. The balloon is then inflated and tested for leakage, as is done before each procedure. A tendency will be noted to inflate more to one side. This is of no practical significance, for within the cervical canal pressure is equalized and the balloon molds itself according to the contour.

The balloon is inflated with water, rather than air, because it is easier to measure and less likely to leak.

Only Luer Lok syringes are used. Glass-tipped syringes break off too easily.

The inflation stem *(Q4)* is positioned to the left or right of the cannula depending upon whether the operator is right- or left-handed. The stem is shown being rotated to the left for a right-handed operator in Fig. 2. Set screws (*e* and *f*) have been loosened and the index finger about the trigger is extended to hold the stem level until the set screws are retightened. Rotation is by means of the free hand at valve *(M)*. This would be reversed for a left-handed operator.

The balloon, like rubber acorn obturators, does not transmit impulses to the kymograph through the cannula. After inflation, it is a plug within the cervical canal. Whether it will transmit cervical or uterine contractions independently through valve *(M1)* to a second recording device is being studied.

A very desirable safety feature is provided by the balloon. If the pressure within the uterine canal builds up dangerously beyond the pressure in the balloon (approximately 250 mm. Hg.), CO_2 or contrast medium escapes automatically around it.[6] A simple turn of valve (*M1*) also releases pressure immediately.

Technique.—The patient is previously prepared as for any sterile vaginal procedure, and placed in slight Trendelenburg position. The cervix is painted with ethyl alcohol, 70 per cent, and the cervical canal is swabbed with cotton applicators dipped in alcohol.

Good exposure and lighting of the cervix are essential for satisfactory technique (Figs. 3 and 4).

Sterilization.—All parts, including the inflatable tip with balloon attached, may be boiled, with the exception of the Hyams plastic tips. These are sterilized only by soaking them and their connectors *(Y)* in aqueous Zephiran 1:1,000 for twenty-four hours. This is not impractical because they are stored indefinitely in this solution without damage to the tips.

Summary

Interchangeable malleable and flexible tips for the self-retaining trigger cannula are presented for use in tubal insufflation and uterosalpingography with rubber acorn obturators, including a new giant acorn. A new inflatable

tip for intracervical obturation is described with a technique for its use in a self-retaining manner with or without the traction tenaculum. Also presented are tips for hysterometry and endometrial biopsy.

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Department of Reviews and Abstracts

Selected Abstracts

Abortions

O'Donnell, Ward M.: Postabortal Oliguria, J. A. M. A. **140**: 1201, 1949.

The author reports three cases of abortion in which oliguria developed. In all these cases abortion had been done before the sixteenth week of pregnancy and none of the patients had a history of previous renal disease. In each the oliguria was of severe degree and was accompanied by headache, malaise, and vomiting—the characteristic manifestations of the crush syndrome. The pathologic findings in the kidneys in all three cases were typical of lower nephron nephrosis; in the case with the longest survival period, there was the most tubular epithelial regeneration and the greatest degree of inflammatory infiltration. The liver showed zonal necrosis in all cases, and two of the patients were jaundiced during life. The uterus in each case contained masses of retained decidua and chorionic epithelium; some of the placental tissue was necrotic, but other portions of the placenta were living and were bathed in maternal blood. Lower nephron nephrosis may be a complication of abortion more frequently than a review of the literature indicates. The development of the renal lesions may be due to a hypothetic precipitating factor (nephrotoxic substance) derived from "dead or dying" placental tissue, associated with the septic state of the patient. Early evacuation of the uterus appears to be indicated in nonseptic abortion with associated oliguria; it is also indicated in septic abortion, as soon as operability is established.

HARVEY B. MATTHEWS

Anesthesia, Analgesia

Greene, Barnett A., and Goldsmith, Morris: Obstetrics for the Anesthesiologist, Anesthesiology **11**: 110, 1950.

On the basis of their experience with caudal or spinal analgesia during labor and delivery in 1,000 cases, the authors outline the obstetrical information that is of special value to the anesthesiologist in the use of this type of anesthesia in obstetrics. The decision as to when to start the administration of caudal analgesia must be made by the anesthetist. While no rigid rules can be formulated, experience has shown that, in primiparas, with an occiput anterior presentation, caudal analgesia usually should not be begun until the vertex of the fetus is one fingerbreadth below the level of the ischial spinous process, the uterine contractions occur every five minutes at least, and the cervix is dilated to three fingerbreadths. If the level of the fetal head cannot be accurately determined, the anesthetist should wait until pains occur every three minutes; the timing of the contractions should be determined by the rectal examination by the anesthetist. In multiparas, caudal analgesia may be begun earlier, when the vertex is at the level of the ischial spines or sacrospinous ligaments, if the presentation is occiput anterior, and uterine contractions occur every five minutes, and the cervix is dilated at least two fingerbreadths. If an occiput posterior presentation is present during the late first stage or early second stage, rotation is less likely to occur if caudal or spinal analgesia is used at this time, be-

cause of changes in the forces of labor caused by this type of analgesia, especially the relaxation of the levator ani. With a posterior or transverse vertex presentation, caudal analgesia is withheld until the vertex definitely passes the spines, even in multiparas and if uterine contractions are occurring every three minutes. General analgesics and sedatives may be used in these cases, until caudal analgesia can be instituted. In breech presentations caudal or spinal analgesia should not be used until the maximum transverse diameter of the breech is below the "spines." Placenta previa is a definite contraindication to caudal or spinal anesthesia. Caudal analgesia is of special value for patients with toxemia or cardiorenal disease, but must be administered in these patients with special care. If the patient lies on her side for caudal analgesia, the cervix may dilate more on its lower than on its upper aspect; the patient should be turned on her other side to aid dilatation of the sluggish part of the cervix. Delay in the progress of labor may be overcome by the anesthetist's directing the patient to bear down when he palpates a uterine contraction. When the patient is transferred in the delivery room from the stretcher to the delivery table, there is often a fall in blood pressure which may be an indication for the intravenous or intramuscular injection of ephedrine sulfate or Neosynephrin hydrochloride; if this is the case, the anesthetist must make certain that the oxytocic subsequently used by the obstetrician does not contain the vasopressor factor present in whole extracts of the posterior pituitary gland, such is Pituitrin.

HARVEY B. MATTHEWS

Gynecology

Frank, Robert T.: Operative Vs. Nonoperative Procedures for Uterine Fibroids, J. A. M. A. **140:** 1001, 1949.

In an unselected series of 3,000 gynecological patients, 916, or 30.5 per cent had uterine fibroids. The most frequent and characteristic symptoms were excessive bleeding, prolonged bleeding, or too frequent uterine bleeding. There were only six cases in the 916 cases of uterine fibroids in which an emergency operation was required, and in only two of these cases was the emergency due to the fibroids themselves. Differential diagnosis between fibroids and pregnancy, corpus or cervical carcinoma, and functional bleeding must be established by pregnancy tests, cytological study of vaginal and cervical smears, hysterograms, response to diethylstilbestrol, and eventually by dilatation and curettage. Small fibroids, especially those that are subperitoneal and fundal, rarely interfere with pregnancy; if pregnancy occurs when the uterus contains such small fibroids, the patient should be carefully watched, especially up to the fourth month of gestation. If at that time the entire uterine mass does not exceed the size of a six to six and one-half months' fetus, the course of pregnancy may be expected to be normal. But if the fibroid mass is cervical or has attained the size of a five months' fetus by the second month of pregnancy, myomectomy is advised during pregnancy. In a detailed study of 464 cases in this series, patients were classified in groups according to the size of the uterus; in the group in which the enlargement of the uterus did not exceed the size of an eight weeks' pregnancy, operation was done or recommended in 45.8 per cent; 54.2 per cent were kept under observation. In the group in which the size of the uterus was the size of a two to four months' pregnancy, operation was indicated in 60.3 per cent; in the group in which the uterus was larger than a four months' pregnancy, operation was indicated in 81.6 per cent. Hysterectomy was done in 72 per cent of this latter group. In some cases, especially in the first group, dilatation and curettage or myomectomy was done. In other cases dilatation and curettage and radium or roentgen-ray therapy were indicated, especially in "poor risk" patients, those with cardiorenal or pulmonary disease or those who were obese. In the 358 hysterectomies done there was one postoperative death—the twenty-seventh case in the series; in the last 331 hysterectomies, no death occurred. Supravaginal hysterectomy is considered by the author to be the operation of choice in nonmalignant conditions, and he has never seen a stump carcinoma develop in any of his

cases, but care is taken to restore the cervix to normal by appropriate treatment before operation. In determining indications for treatment in cases of small fibroids, it is noted that, at the menopause, fibroids up to the size of a three months' fetus tend to involute and disappear; such involution is delayed by the premature administration of estrogens. On the basis of his study of this series the author concludes that the tendency in the present treatment of uterine fibroids is still "too radical" and operation is done too often.

HARVEY B. MATTHEWS

Reynolds, Roland P., Owen, Clarence I., and Cantor, Meyer O.: Arteriovenous Aneurysm of Uterine Artery and Vein, J. A. M. A. **141:** 841, 1949.

The authors report a case of cirsoid aneurysm of the myometrium, in which an attempt at curettage caused severe uterine hemorrhage. A supracervical hysterectomy was done promptly; five hours later the abdomen was reopened and a vessel in the broad ligament, which was the source of bleeding, was clamped and tied; the patient made a good recovery. Two other cases of this type of uterine aneurysm were found reported in the literature. One of these patients died postoperatively and the other developed hemiplegia on the seventh day after operation. All these three cases have certain features in common. The uterus was soft; the blood vessels of the broad ligaments and of the uterus were dilated, tortuous, and showed pronounced thickening of their walls; there was marked fibrosis of the myometrium and of the cystic glands of the cervix. In one of the reported cases, as in the authors' case, dilatation of the cervix for curettage caused profuse hemorrhage. This procedure is definitely contraindicated if the diagnosis of cirsoid aneurysm of the myometrium is suspected.

HARVEY B. MATTHEWS

Mazza, Miguel, and Foix, Antonio: Referred Shoulder Pain in Gynecology, Obst. y ginec. latino-am. **7:** 85, 1949.

Shoulder pain of genital origin, usually described in gynecology in connection with ruptured tubal pregnancy, may occur in a variety of acute and chronic gynecologic diseases. It is a referred type of pain, originating from the affected pelvic viscus, and interpreted in terms of corresponding segmental innervation. The presence of free blood in the peritoneal cavity is not necessary for its production. This is demonstrated by the occasional occurrence, in tubal pregnancy, of shoulder pain as an initial symptom preceding signs of tubal rupture; and by disappearance of the referred pain after excision of the affected viscus, even though free blood remains in the peritoneal cavity. In one of their patients, the authors were able to produce typical shoulder pain by pinching the Fallopian tubes at laparotomy under spinal anesthesia. The literature is briefly reviewed.

DOUGLAS M. HAYNES.

Vieira, Abel V.: Genital Tuberculosis, Bol. Soc. chilena de obst. y ginec. **14:** 130, 1949.

During 1947 and 1948, there were 1,710 gynecologic patients admitted to the author's service, 225 of whom presented adnexal or peritoneal lesions. A definitive diagnosis of genital tuberculosis was made in 33 of these patients, representing 1.9 per cent of all admissions and 14.7 per cent of patients with pelvic inflammatory disease. Forty-nine per cent of the patients were in the third decade of life, but only one patient was older than 40 years. The most prominent presenting menstrual complaint was dysmenorrhea, recorded in 21 per cent; 18 per cent of the women had amenorrhea; 49 per cent had no menstrual abnormality. One-half the patients gave a previous history of tuberculosis, but only 6 per cent had active tuberculosis on admission. Sixty per cent of the patients were in excellent general physical condition. Eighty per cent gave a history of sterility. The commonest presenting symptom was pelvic pain, present in 88 per cent of the patients;

24 per cent had febrile manifestations. The diagnosis was established by endometrial biopsy in 86 per cent of the cases, the remaining diagnoses being postoperative pathologic findings.

The author believes that the advent of streptomycin therapy will greatly modify the hitherto largely surgical approach to the problem of genital tuberculosis.

DOUGLAS M. HAYNES.

Labor, Management, Complications

Stamer, S.: On Induced Labor, Acta obst. et gynec. Scandinav. **29**: 101, 1949.

Experience with induction of labor over a five-year period at the Rigshospital in Copenhagen is reviewed. Of 805 patients induced, 48 per cent went into labor with medical induction alone. Indications for induction were broad, including particularly contracted pelvis and oversized fetus. Labor was as readily induced in primigravid women as in parous patients. Once induced, labor progressed more rapidly in women receiving medical induction alone than in those in whom the membranes were artificially ruptured. Fetal size and maternal age were without influence on effectiveness of induction. There was minor puerperal morbidity in 46 patients, in nearly all of whom amniotomy had been employed. Five instances of prolapsed cord were observed, all following artificial rupture of membranes. Fetal mortality was 3.7 per cent for the series (29 deaths). No death was attributable to purely medical induction, whereas, in 5 of 21 fetal deaths, amniotomy may have contributed to the fatal outcome. The author concludes that induction of labor is most safely accomplished by medical means alone.

DOUGLAS M. HAYNES.

Hartnett, Leo J., and Freiheit, Harold J.: Curare as an Adjunct in the Conduct of Labor, South. M. J. **43**: 277, 1950.

When curare is administered parenterally to man there is a regular sequence which occurs in skeletal muscle paralysis. First, muscles of the eyelid and eyeball are affected, next the facial muscles and the muscles of the neck, with resulting head drop and difficulty of speech. The muscles of the trunk, perineum, and extremities are depressed and finally paralysis of the diaphragm occurs. Relaxation of the perineum facilitates the spontaneous expulsion of the term fetus and, if this can be accomplished without danger to the mother or fetus, curare could be a useful adjunct to the conduct of labor. The author administered curare in a dose of 20 units of Intocostrin intravenously during the second stage of labor. The response to medication was noted by relaxation of the perineum and gauged clinically and measured clinically by relaxation of the anal sphincter. Response was usually observed within 40 seconds. Satisfactory relaxation of the perineum occurred in 91 per cent of the patients. Spontaneous delivery occurred in 79 per cent of all cases and was accomplished without anesthesia in 86.5 per cent. It is thought that the analgesic effect of curare may be due to some blocking effect on the afferent sensory fibers. No effect was observed upon the rate or intensity of uterine contractions.

In the discussion of this paper, concern was expressed for the dangers incident to the use of curare in labor. It is recommended that the drug be used only in hospitals where a trained anesthesiologist is responsible for its administration.

WILLIAM BICKERS.

Newborn

Ranstrom, Stig, and Vom Sydow, Gert. Rickets in Newborn Infants. Clinical and Histologic Study, Pediatrics **4**: 406, 1949.

This clinical and histologic study of rickets in the newborn was undertaken by the Medical Department of the Childrens' Hospital, Gothenburg, and the Department of Pathology, University of Uppsala, Uppsala, Sweden.

In a series of 181 consecutive cases of infants who had died soon after birth, one to sixteen days, 103, or 56.9 per cent, showed definite histologic signs of rickets. Of the 69 infants dying during the first day of life, 20, or 29 per cent, had rachitic changes and in these the rickets must be regarded as congenital. Of the 181 infants, 154 were premature, weighing less than 2,500 Gm. at birth. The incidence of rickets was about the same in the premature and the full-term infants in this material. The incidence of rickets increases rapidly with increasing age during the first weeks of life.

These observations may be of practical importance in that they transfer a larger amount of the responsibility for the prevention of rickets to the obstetrician than hitherto.

JAMES P. MARR, M.D.

Illingworth, R. S.: Birth Weight and Subsequent Weight, Brit. M. J. 1: 96, 1950.

The weight of 1,343 children observed at intervals during the first three years of life was correlated with the recorded birth weight. The results of this study which were considered statistically significant indicated that the birth weight could be employed to project the weight during this period. Boys consistently averaged more in weight as compared to girls. In general the greater the birth weight the more the child would weigh at one, two, and three years, respectively. It is concluded that a considerable proportion of so-called underweight children are found to be of average weight when due attention is paid to age, sex, and birth weight.

R. GORDON DOUGLAS.

Ruch, Walter A.: A Comparison of Rooming-in Versus Standard Nursery Technic, South. M. J. 43: 181, 1950.

The "rooming-in" plan for care of newborns is receiving much interest by laymen and physicians. It is thought that the newborn infant should be treated in every way as a new patient admitted by way of the delivery room. Placing the baby in the room with its mother is important from a psychological standpoint. It has been said that the psychologic adjustment of the baby during the first few days of life is all important in determination of its future personality characteristics. The rooming-in plan eliminates the danger of cross infection in large nurseries, avoids the transportation of babies through corridors, and eliminates the mechanical difficulties of bringing infants to the bedside of the mothers. A questionnaire sent to mothers who had experienced the new system for baby care gave a 97 per cent positive approval for the plan.

It is quite possible that future hospital construction must take into account this new trend in care of the newborn.

WILLIAM BICKERS.

Gerver, Joan M., and Day, Richard: Intelligence Quotient of Children Who Have Recovered From Erythroblastosis Fetalis, J. Pediat. 36: 342, 1950.

This report from the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York, is an attempt to discover if there are children surviving erythroblastosis fetalis, who suffer from mild impairment of mentality, in addition to the well-recognized group who exhibit residual severe motor disability.

The average intelligence, as measured by the Stanford-Binet Scale, of a group of sixty-eight children recovered from erythroblastosis fetalis without suffering obvious motor-nerve damage was found to be lower than that of their unaffected older brothers and sisters. Statistical analysis indicated that the inferiority is not likely to have resulted from chance nor from the circumstance that the affected child was always younger than his control sibling. The extent of the impairment is slight, the mean difference in I.Q. being only 11.8, so that there is no occasion for altering the usual custom of giving

a good prognosis to the parents of a child who has apparently recovered from erythroblastosis without suffering motor-nerve injury.

The data presented do not distinguish between a specific effect of the Rh antibody and a nonspecific one such as might be operating in any illness in the newborn period.

JAMES P. MARR.

Massler, Maury, and Savara, Bhim Sen: Natal and Neonatal Teeth, A Review of Twenty-Four Cases Reported in the Literature, J. Pediat. **36:** 349, 1950.

The authors from the University College of Dentistry in Chicago present this informative paper on natal and neonatal teeth in order to establish the present status of our knowledge of this problem. The question of the normality of the structures and whether such prematurely erupted teeth should be retained or extracted are questions of interest to the obstetrician and more especially to the pediatrician.

A search through the literature revealed only twenty-four such cases. The incidence is reported as occurring once in 2,000 births in two Chicago hospitals.

There is strong tendency for natal and neonatal teeth to be merely prematurely erupted lower central incisors (usually both). The strong predilection for the lower central incisors is not surprising in view of the fact that these teeth are normally the first to erupt into the oral cavity.

There were six complications due to erupted teeth, the most common being refusal to nurse and injury to maternal nipples. Three cases proved fatal due to uncontrolled bleeding and infection from a lacerated gingiva or necrosis of the alveolar process.

The authors advise against indiscriminate extraction of these teeth in spite of reported fatalities.

With the exception of the familial tendency, all other factors can be discarded easily as unsatisfactory explanations or causes for the phenomenon of natal and neonatal teeth.

JAMES P. MARR.

Strain, James E., and Connell, John R.: Pneumothorax in the Newborn Infant, J. Pediat. **36:** 495, 1950.

A case report from the Children's Hospital and the Department of Pediatrics, Colorado University School of Medicine, Denver, deals with a premature child delivered by cesarean section, who developed a pneumothorax on the fourth postoperative day.

The etiology of this complication, when not due to external trauma, is somewhat obscure. Rupture of giant lung cysts, lung aplasia, and pulmonary infections are not uncommon findings. The authors are of the opinion that the principal cause of pneumothorax in the newborn is related to the pneumodynamics of the alveolar sacs. Increased pressure within the lungs causes rupture of peripheral emphysematous blebs into the pleural cavities with development of pneumothorax.

The prognosis depends largely upon the severity of the symptoms. It is poor in those developing pneumothorax at or shortly after birth. A 42 per cent mortality has been reported by DeCosta.

The treatment of choice in those patients developing pneumothorax late is usually conservative; i.e., oxygen, carbon-dioxide inhalations, and prophylactic penicillin.

Early recognition of the existence of pneumothorax by the cardinal symptoms of increasing dyspnea and gradual cyanosis shortly after birth, together with x-ray corroboration, may be lifesaving in those infants requiring aspiration.

JAMES P. MARR.

Pregnancy, Complications

Laforet, C. Colmeiro: Appendicitis and Pregnancy, Rev. clin. espãn. **34:** 110, 1949.

In reviewing the world literature since 1911, the author finds the reported incidence of appendicitis in pregnancy to average 1.02 per 1,000. Appendicitis is most frequently

encountered during the latter half of pregnancy. Gangrenous appendicitis and appendiceal perforation are, respectively, 5 and 3 times more common during pregnancy than otherwise, presumably because of less prompt recognition consequent to complication of the differential diagnosis by topographical changes and symptomatology of pregnancy. Over-all average maternal mortality varies from 0.71 per cent in localized appendicitis to 30 per cent in secondary peritonitis. Abortion or premature labor has been reported in from 11.4 to 33 per cent of localized appendicitis, in from 55.6 to 72 per cent of peritonitis, and in 66 per cent of appendiceal abscess. Definitive treatment is prompt appendectomy, at which concomitant obstetrical or other surgical procedures must be strictly avoided.

DOUGLAS M. HAYNES.

Bunim, Joseph J., and Appel, S. Baer: A Principle for Determining Prognosis of Pregnancy in Rheumatic Heart Disease, J. A. M. A. **142:** 90, 1950.

From 1939 to 1948, 205 women with rheumatic heart disease were observed during pregnancy and the puerperium at Bellevue Hospital. In this period, pregnancy was interrupted in 11 other women with rheumatic heart disease, because the prognosis was considered unfavorable. There were 299 babies delivered, including 6 pairs of twins; 2 women died undelivered. In 122 cases delivery was spontaneous, in 68 by forceps, in 9, breech deliveries; cesarean section was done in 6 cases, but only on definite obstetric indications. There were 3 deaths in the entire series, but no deaths from congestive heart failure in women who were under the authors' care throughout pregnancy and the puerperium. Congestive cardiac failure developed during pregnancy in 36 of the 205 women, or 17.6 per cent; failure occurred most frequently in the second half of pregnancy. In those cases in which the duration of rheumatic disease could be determined (interval of time from the onset of the first rheumatic manifestations), it was found that only 4 per cent of those who had rheumatic disease for less than ten years developed cardiac failure, while 37 per cent of those with a duration of the disease over twenty years became decompensated during pregnancy. The average age of the group in whom cardiac failure developed was greater than in the group without failure. Another important factor was the cardiac reserve before pregnancy. Thus of 118 patients in Classes 1 and 2 (New York Heart Association classification) only 4 developed cardiac failure during pregnancy, while failure occurred in 32 of 87 patients in Classes 3 and 4. A history of previous cardiac failure was also of importance. Pregnancy as such was not found to alter the course of rheumatic heart disease. The indication for interruption of pregnancy in the 11 cases in which this was done (per vaginam) were based on the study of the factors which affect the prognosis or rheumatic heart disease *per se* especially the functional capacity and history of previous failure.

HARVEY B. MATTHEWS.

Items

American Board of Obstetrics and Gynecology

The annual meeting of the Board was held in Atlantic City, N. J., from May 21 to 27 inclusive, 1950, at which time 259 candidates were certified.

New Bulletins, incorporating changes made at the recent meeting, are now ready for distribution. These changes include adoption of a special form to be designated as the "Appraisal of Incomplete Training Form" which will be forwarded to prospective applicants upon request. Numerous changes concerning graduate training in obstetrics and/or gynecology have also been adopted and will be of special interest to hospitals conducting residency programs as well as to prospective applicants to this Board.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 2, 1951. Application may be made until Nov. 5, 1950. Application forms and Bulletins are sent upon request made to

PAUL TITUS, M.D., Secretary
1015 Highland Building
Pittsburgh 6, Pa.

Diplomates

Candidates certified at annual meeting and examinations, American Board of Obstetrics and Gynecology, Inc., May 21 to 27, 1950:

Aaron, Jules Bryan	1333 President Street	Brooklyn, N. Y.
Adams, Wendall W.	10465 Carnegie Avenue	Cleveland, Ohio
Akers, Elwyn Nickell	Letterman General Hospital	San Francisco, Calif.
Allison, Harold McW.	206 East North Street	Greenville, S. C.
Avner, Saul Leighton	Oliver General Hospital	Augusta, Ga.
Bacon, William Benj.	420 Warren Street	Brookline, Mass.
Bahl, Charles D.	2449 Gilbert Avenue	Cincinnati, Ohio
Baker, Milton Ernest	1409 Willow Street	Minneapolis, Minn.
Baker, William S., Jr.	U. S. Naval Hospital	Camp LeJeune, N. C.
Ball, Thomas L.	321 Hollywood Avenue	Douglaston, L. I., N. Y.
Ballentine, George N.	416 Pine Street	Williamsport, Pa.
Barrow, Leonard A.	Hart-Albin Building	Billings, Mont.
Beck, Harry McB.	700 North Charles Street	Baltimore 1, Md.
Benigno, Benedict B.	140 East 54th Street	New York 22, N. Y.
Benjamin, Joseph F.	203 Godwin Avenue	Ridgewood, N. J.
Bennett, Robert Edward	44 Pearl Street	Worcester, Mass.
Berk, Alexei N.	36 Gramercy Park	New York 3, N. Y.
Bevan, John Yocum	401 Market Street	Steubenville, Ohio
Bibbs, John Donald	14717 Detroit Avenue	Lakewood 7, Ohio
Bilotta, Walter A.	1657 Tenth Avenue	Brooklyn, N. Y.
Bogen, Ben	173 Westminster Road	Brooklyn 18, N. Y.
Boso, Clarence H.	421½ Eleventh Street	Huntington, W. Va.
Branaman, Guy H.	500 St. Mary's Street	Raleigh, N. C.
Bresin, Bernard P.	10616 Euclid Avenue	Cleveland 6, Ohio
Bringle, Carey Gaines	188 South Bellevue	Memphis, Tenn.
Brown, William W., Jr.	1307 Amicable Building	Waco, Tex.
Bumgardner, Heath D.	3701 North Broad Street	Philadelphia 40, Pa.

Burch, John E.	607 Main Street	Joplin, Mo.
Bushnell, Lowell F.	4759 Hollywood Boulevard	Los Angeles, Calif.
Cadden, Edward Robert	417 Heyburn Building	Louisville, Ky.
Callender, Claude G.	727 Carlisle Street	Jackson, Miss.
Carmichael, Josiah C.	1117 South 22nd Street	Birmingham, Ala.
Carrington, Elsie R.	3401 North Broad Street	Philadelphia 40, Pa.
Carsen, Albert J.	48 East Santa Clara	San Jose, Calif.
Cartnick, Edward N.	821 Franklin Avenue	Garden City, L. I., N. Y.
Caruso, Lawrence Jos.	114 East 72nd Street	New York 21, N. Y.
Casey, William R.	957 Delaware Avenue	Buffalo 9, N. Y.
Cestero, Angel Rafael	Box 282	Rio Piedras, Puerto Rico
Childs, Milford	74 Linwood Avenue	Buffalo 9, N. Y.
Chinn, Raymond F.	1801 K Street, N.W.	Washington, D. C.
Clever, John Edward	1015 Highland Building	Pittsburgh 6, Pa.
Cody, Melville Lockett	6410 Fannin Street	Houston, Tex.
Cohn, Sidney	1078 Madison Avenue	New York, N. Y.
Collins, Jason Haydel	Ochsner Clinic 3503 Prytania Street	New Orleans, La.
Commings, Pete	Gallinger Municipal Hospital	Washington, D. C.
Coudon, Joseph	508 Greenleaf Building	Jacksonville, Fla.
Crawford, Sterling T.	525 N. W. Eleventh Street	Oklahoma City 3, Okla.
Cunningham, Thomas R.	5159 South Damen Avenue	Chicago 9, Ill.
Cushing, Robert M.	502 Park Avenue	New York 22, N. Y.
Davis, Julius T., Jr.	4414 Magnolia Street	New Orleans, La.
Demas, Nicholas Wm.	127 East Acacia Street	Stockton, Calif.
Dennis, Melvin S.	7301 Schaefer Road	Dearborn, Mich.
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Doeller, Chas. H., Jr.	1025 North Calvert Street	Baltimore 2, Md.
Dougherty, Cary M.	3369 Convention Street	Baton Rouge, La.
Duffy, William C.	1120 St. Paul Street	Baltimore 2, Md.
Ehrlich, Harry	550 Ocean Avenue	Brooklyn, N. Y.
Elzey, Neil Douglas	Woodland Clinic	Woodland, Calif.
Eschbach, Joseph Wm.	935 South Military	Dearborn, Mich.
Estes, Woodrow Brown	700 Sixth Avenue, South	St. Petersburg, Fla.
Farris, Louis G.	894 Colvin Avenue	Kenmore, 17, N. Y.
Fee, Manson G.	311 Kresge Building	Flint, Mich.
Fiorello, Joseph R.	689 Princeton Avenue	Trenton, N. J.
Fisher, Robert L.	Sharon Clinic	Sharon, Conn.
Foley, Thomas Henry	1934 East 18th Avenue	Denver, Colo.
Forman, Joseph B.	New Haven Hospital	New Haven, Conn.
Fouche, Heyward H.	1412 Bull Street	Columbia, S. C.
Freeman, Donald W.	University of Minnesota The Medical School	Minneapolis 14, Minn.
Freeman, John Joseph	4 North Cicero Avenue	Chicago, Ill.
Gardner, Irvin B.	411 Primrose Road	Burlingame, Calif.
Gardner, Milton M.	98 Wolcott Road	Hicksville, N. Y.
Gayle, John Ferguson	171 Armstrong Drive	Hampton, Va.
Gehret, Andrew Martin	1007 Park Place	Wilmington 19, Del.
Gibson, William Edward	1010 Center Street	Pittsburgh 21, Pa.
Gil Rivera, Rafael A.	City Hospital	San Juan, Puerto Rico
Gillick, William C.	927 Ferry Avenue	Niagara Falls, N. Y.
Goforth, Mabel L.	1326 Madison, Medical Center	Seattle 4, Wash.
Goins, William F.	3400 McDougall Street	Detroit, Mich.
Gold, Isadore Roy	470 Ocean Avenue	Brooklyn 26, N. Y.
Goldstein, Leopold Z.	1715 Spruce Street	Philadelphia, Pa.
Graffagnino, Peter C.	1100 Third Avenue	Columbus, Ga.
Grandin, Dean J.	1088 Park Avenue	New York 28, N. Y.
Gray, David Earle	910 National Reserve Building	Topeka, Kan.
Gray, Lee	1421 State Street	Santa Barbara, Calif.
Green, Naomi	136 South 16th Street	Philadelphia 2, Pa.
Greene, Irving	2755 University Avenue	New York, N. Y.
Greer, James Matthew	170 Maple Avenue	White Plains, N. Y.
Griffin, Jack B.	4407 Oak Lawn	Dallas, Tex.
Griffith, Mary Irene	420 West Fourth Street	Winston-Salem, N. C.
Grossman, John Henry	144 Golden Hill Street	Bridgeport 3, Conn.
Haigh, John Sigmund	1405 San Marino Avenue	San Marino 9, Calif.
Haley, John C.	59 Trumbull Street	New Haven 10, Conn.
Hall, Donald William	216 Summer Street	Buffalo 9, N. Y.

Hamlin, Charles H.	85 Jefferson Street	Hartford, Conn.
Hanlon, Paul Adrian	Deposit & Savings Bank Bldg.	Wilkes-Barre, Pa.
Hanson, Walter N.	U. S. Naval Hospital, Santa Margarita Ranch	Oceanside, Calif.
Harkins, James Edwin	4456 39th Avenue	Oakland 19, Calif.
Harrison, Harry Luke, Jr.	48 East Santa Clara Street	San Jose, Calif.
Haus, Loren Wilson	1319 Austin Street	Houston, Tex.
Haverty, Edwin A.	328 Mamaroneck Avenue	White Plains, N. Y.
Hawke, Clarence M.	128 Locust Street	Harrisburg, Pa.
Hehn, Arthur Clarence	331 Lenox Road	Jenkintown, Pa.
Heiberger, Charles J.	Jefferson Building	Peoria, Ill.
Hein, Richard James	947 West Eighth Street	Los Angeles 14, Calif.
Henderson, Charles W.	3001 West Grand Boulevard	Detroit 2, Mich.
Henderson, Wayne B.	535 Date Street	San Diego, Calif.
Henry, Walter John	Pleasant and Bennett Streets	Bradford, Pa.
Hess, Orvan W.	79 Trumbull Street	New Haven, Conn.
Heywood, Leo T.	1307 Medical Arts Building	Omaha, Neb.
Hill, Frank A.	221 South Fourth Street	Grand Forks, N. D.
Hood, Marianna	4227 Herschel Street	Dallas, Tex.
Hughes, Victor A.	217 West Ashley Street	Jacksonville, Fla.
Humphrey, Henry Daniel	114 West Buffalo Street	Ithaca, N. Y.
Hunter, James S., Jr.	102-110 Second Avenue, S.W.	Rochester, Minn.
Hunter, Robert MacA.	250 South 18th Street	Philadelphia 3, Pa.
Hynes, John E., Jr.	208 Hart-Alben Building	Billings, Mont.
Jewett, John Figgis	319 Longwood Avenue	Boston 15, Mass.
Johnson, Donald G.	525 East 68th Street	New York 21, N. Y.
Kannapel, Allen Robert	250 South 18th Street	Philadelphia 3, Pa.
Kardash, Theodore	114 Medical Arts Building	Baltimore 1, Md.
Keeler, James E.	227 Plaza Medical Building	Kansas City, Mo.
Kelly, Robert Francis	2202 West Third Street	Los Angeles 5, Calif.
Kernodle, John R.	Alamance General Hosp., Inc.	Burlington, N. C.
Kime, James Sellers	156 West Humboldt Parkway	Buffalo 14, N. Y.
King, Tom C., Jr.	313 East Tenth Street	Anniston, Ala.
Kleinman, Herman	1412 50th Street	Brooklyn 19, N. Y.
Knoch, H. Kermit	1103 Grand Avenue	Kansas City, Mo.
Kohut, George John	U. S. Naval Hospital	Pensacola, Fla.
Kramm, August	804 Farragut Medical Building	Washington 6, D. C.
Krosnick, Gerald	38 Trumbull Street	New Haven, Conn.
Lancaster, George Gale	960 East Green Street	Pasadena 1, Calif.
Landesman, Robert	20 East 67th Street	New York, N. Y.
Langsam, Sanford Martin	1301 Cornaga Avenue	Far Rockaway, L. I., N. Y.
Lash, Sidney R.	30 North Michigan Avenue	Chicago, Ill.
Lauck, Robert E., Jr.	315 South Broadway	Tyler, Tex.
Lavine, William	2021 Grand Concourse	New York, N. Y.
Lawrence, Lucy K.	311 Bank of America Bldg.	Whittier, Calif.
LeCocq, Frank, Jr.	13 South Twelfth Avenue	Yakima, Wash.
Ledfors, Gustave E.	2020 Arroyo Drive	Riverside, Calif.
Leibfried, Jane M.	5501 Greene Street	Philadelphia 44, Pa.
Levy, Charles K.	706 Decatur Street cor. Hopkinson Avenue	Brooklyn 33, N. Y.
Lewis, Charles F., Jr.	431 30th Street	Oakland, Calif.
Lidikay, Edward Cline	915 Hume Mansur Building	Indianapolis, Ind.
Linn, G. Graham	10515 Carnegie Avenue	Cleveland, Ohio
Liswood, Jacques	8415 Bay Parkway	Brooklyn, N. Y.
Loeff, Harold M.	55 East Washington Street	Chicago 2, Ill.
Long, Joseph Pote	1930 Chestnut Street	Philadelphia 3, Pa.
Long, Robert C.	806 Heyburn Building	Louisville 2, Ky.
Loomis, Robert Osborn	608 East Genesee Street	Syracuse, N. Y.
Luria, Sydney	881 Lafayette Street	Bridgeport, Conn.
Mahoney, Hugh Francis	9 Central Street	Lowell, Mass.
Mallin, Lloyd P.	Commonwealth Building 2010 East 102nd Street	Cleveland 6, Ohio
Meyerhoff, Kurt H.	947 State Street	Schenectady, N. Y.
Mickal, Abe	1413 Richards Building	New Orleans 12, La.
Miller, Jack G.	St. Charles Clinic	St. Charles, Mo.
Mills, Charles W.	1004 Livesley Building	Salem, Ore.
Mitchell, George W., Jr.	Harrison and Bennet Streets	Boston 11, Mass.
Mixson, William Chas.	320 West 47th Street	Kansas City 2, Mo.

Monat, Seymour	15 North Brentwood	Clayton 5, Mo.
Morrison, Donald Wm.	875 Main Street	Manchester, Conn.
Morrison, John Huff	6 East Read Street	Baltimore 2, Md.
Morton, James F.	634 Market Street	Zanesville, Ohio
Muller, Paul F.	3311 North Meridian Street	Indianapolis 8, Ind.
Mulligan, William Jos.	32 Cumberland Avenue	Brookline, Mass.
Murray, Stephen Ebe	134 North Third Street	Easton, Pa.
McCaffrey, Fabian J., Jr.	100 East Franklin	Minneapolis 4, Minn.
McCall, John Oppie, Jr.	812 S.W. Washington Street	Portland 5, Ore.
McCann, Charles D.	12 Cottage Street	Brockton, Mass.
McCarthy, Eugene G.	Plainview Sanitarium	Plainview, Tex.
McGinnis, William F.	3720 Washington Avenue	St. Louis 8, Mo.
McGrane, James Leo	1217 Union Street	Schenectady, N. Y.
McNicholas, John R.	645 Catterlin Avenue	Salem, Ore.
Neumann, Gottfried	784 Park Avenue	New York, N. Y.
Nichols, Ervin Edson	1405 San Marino Avenue	San Marino, Calif.
Niles, George A., Jr.	18 Fourth Street, N.W.	Atlanta, Ga.
Nolan, David M.	2811 Pennsylvania Ave., S.E.	Washington 20, D. C.
Pace, Harry R.	4611 Twelfth Avenue	Brooklyn 19, N. Y.
Phalen, James Richard	1651 Fourth Avenue	San Diego 1, Calif.
Phillips, John Barnes	Medical Arts Building, Barrett Street	Schenectady, N. Y.
Picot, Harrison	804 Prince Street	Alexandria, Va.
Portnuff, Joseph Chas.	1538 Sherbrooke Street, Medical Arts Building	Montreal, Canada
Price, Neel Jack	1746 K Street, N.W.	Washington, D. C.
Prince, Leon N.	2647 Reed Street	Philadelphia 46, Pa.
Putterman, Allan	8820 146th Street	Jamaica 2, N. Y.
Raber, Paul A.	Citizens Building	Decatur, Ill.
Rapp, Michael Spilcer	100 Central Avenue	Staten Island 1, N. Y.
Redmon, John J.	1145 Madison Avenue	Memphis, Tenn.
Rhu, Hermann S., Jr.	130 South Scott Street	Tucson, Ariz.
Rich, Joseph	136-36 Sanford Avenue	Flushing, L. I., N. Y.
Ritchie, Douglas C.	205 Tegler Building	Edmonton, Alberta, Canada
Ritmiller, LeRoy F.	George F. Geisinger Memorial Hospital	Danville, Pa.
Robins, Albert Irving	900 17th Street, N.W.	Washington, D. C.
Robinson, Milton	123 East 83rd Street	New York 28, N. Y.
Roehl, Robert H.	3041 Bailey Avenue	Buffalo 15, N. Y.
Rogers, William H.	Lakeview Hospital	Suffolk, Va.
Royals, James Lee	727 Carlisle Street	Jackson, Miss.
Rubricius, Jeanette L.	212 East 72nd Street	New York, N. Y.
Russell, Keith Palmer	511 South Bonnie Brae	Los Angeles 5, Calif.
Salerno, Louis Joseph	Flower Fifth Avenue Hospital 1249 Fifth Avenue	New York, N. Y.
Schadel, Lees M., Jr.	1930 Chestnut Street	Philadelphia 3, Pa.
Schaeffer, Frances C.	26 North Eighth Street	Allentown, Pa.
Schinfeld, Louis Harry	255 South 17th Street	Philadelphia 3, Pa.
Schnall, Meyer DeWitt	130 East 67th Street	New York, N. Y.
Schram, Maxwell	485 Ocean Avenue	Brooklyn, N. Y.
Schudmak, Melvin	2429 Madison Avenue	Baton Rouge, La.
Scott, Eleanor	1014 St. Paul Street	Baltimore 2, Md.
Scott, Joseph Whiddon	1700 Biscayne Boulevard	Miami, Fla.
Seitchik, Joseph Norman	Hahnemann Hospital, 230 North Broad Street	Philadelphia 2, Pa.
Seltzer, Leo Maurice	218 Professional Building	Charleston 9, W. Va.
Settlage, Arnold F. E.	4607½ Crenshaw Boulevard	Los Angeles 43, Calif.
Shannon, Dean Richard	414 Butler Savings and Trust Building	Butler, Pa.
Shea, Samuel Hazen	1801 K Street, N.W.	Washington 6, D. C.
Siegner, Allan Wesp	826 West Delavan Avenue	Buffalo 9, N. Y.
Simpson, Alan Gilbert, Jr.	U. S. Naval Hospital	St. Albans, L. I., N. Y.
Singleton, Virginia A.	1304 Santa Rosa Street	San Luis Obispo, Calif.
Skiles, William V., Jr.	56 Fifth Street	Atlanta, Ga.
Smith, Mary Noble	765 Main Street	Laconia, N. H.
Smolev, Joseph M.	152 Boulevard	Passaic, N. J.
Speert, Harold	622 West 168th Street	New York 32, N. Y.
Spezia, J. L.	1403 Medical Arts Building	Houston, Tex.

Stewart, Donald Mitchell	745 Main Street	Fitchburg, Mass.
Stokes, Elmer Malcolm	1415 East 15th Street	Tulsa, Okla.
Stoltz, Charles Rodney	The Watertown Clinic	Watertown, S. D.
Stone, Oral Henry	2500 West Central	Toledo, Ohio
Strateman, Charles M.	70 East 80th Street	New York, N. Y.
Straub, Joseph John	505 Sixth Street 434 Davidson Building	Sioux City, Iowa
Tandy, Roy W., Sr.	Quantico Naval Hospital	Quantico, Va.
Tappen, Daniel Lloyd	Suite 726 Mills Building	Topeka, Kan.
Taylor, John Champneys	1022 Park Street	Jacksonville, Fla.
Thomas, B. Edmond	147-05 Roosevelt Avenue	Flushing, L. I., N. Y.
Thomas, Herbert Holden	1005 South 21st Street	Birmingham, Ala.
Thomas, Wm. Orville, Jr.	1735 North Wheeler	Portland, Ore.
Todd, Thomas Cabell	510 Cumberland	Bristol, Va.
Tucker, Arthur W., Jr.	32 Cumberland Avenue	Brookline 46, Mass.
Tucker, Jack S.	3221 Fruitvale Avenue	Oakland, Calif.
Vance, Cyril L.	812 Medical Arts Building	Salt Lake City 1, Utah
Vunk, Raymond Hudson	Suite 309 Methodist Hospital	Memphis, Tenn.
Wager, Henry Paul	39 Gifford Avenue	Jersey City, N. J.
Wall, Roscoe Legrand, Jr.	36 Pleasant Street	Worcester 8, Mass.
Wallace, Arthur J.	442 West Lafayette Street	Tampa 6, Fla.
Wallace, Deane DeVere	629 Donaghey Building	Little Rock, Ark.
Watov, Samuel Elias	178 West State Street	Trenton, N. J.
Watson, Stephen Lawton, Jr.	133 South Kentucky Avenue	Lakeland, Fla.
Weekes, Leroy R.	3112 South Western Avenue	Los Angeles 7, Calif.
West, Robert Henry	636 Church Street	Evanston, Ill.
Wiener, William B.	421 Barnett Madden Building	Jackson, Miss.
Williams, Claiborne	Vanderbilt Hospital	Nashville 4, Tenn.
Williams, Philip C.	5626 South Parkway	Chicago 37, Ill.
Williger, Victor M.	104 South Michigan Avenue	Chicago, Ill.
Winheld, Edward B.	1920 Pine Street	Philadelphia, 3, Pa.
Wolff, Herbert Marx	942 West State Street	Trenton 8, N. J.
Woltz, John H. E.	1509 Elizabeth Avenue	Charlotte 4, N. C.
Woodworth, Jess J., Jr.	21871 Lake Shore Boulevard	Euclid 19, Ohio
Younge, Fitzroy Egerton	1716 Market Street	Oakland 7, Calif.
Zaidenberg, Samuel O.	4917 North Avers Avenue	Chicago 25, Ill.
Zeichner, Sidney	960 Sterling Place	Brooklyn, N. Y.
Ziserman, Abraham Jos.	2046 Pine Street	Philadelphia 3, Pa.
Zummo, Bruce Peter	27 South Pulaski Road	Chicago, Ill.
Zweibel, Leonard	871 South 11th Street	Newark, N. J.

Urology Award

The American Urological Association offers an annual award of $1,000.00 (first prize of $500.00, second prize $300.00, and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Palmer House, Chicago, Ill., May 21 to 24, 1951.

For full particulars write the Secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, N. J. Essays must be in his hands before Feb. 10, 1951.

International College of Surgeons

The Fifteenth Annual Assembly of the United States Chapter of the International College of Surgeons will be held in Cleveland, Ohio, October 31 to November 3, with headquarters at the Cleveland Hotel.

Surgical clinics will be held in several Cleveland hospitals on Monday, October 30. All scientific sessions will be held at the Cleveland Public Auditorium 9:00 A.M. to 5:00 P.M., Tuesday through Friday.

At the annual banquet at the Statler Hotel on Thursday evening, Dr. Frank Lahey of Boston will talk on "Some of the Recent Advances in Surgery." Dr. Elmer Henderson, President of the American Medical Association, will deliver an address on "The Importance of International Cooperation in Surgery."

Reservations may be secured by writing to the Committee on Hotels, International College of Surgeons, 511 Terminal Tower, Cleveland 13, Ohio. Preliminary programs may be obtained from the central office, 1516 Lake Shore Drive, Chicago 10, Ill.